MASTER OF DENTAL SCIENCE

Software development for the automatic calculation of dental arch relationships on digital models in cleft lip and palate

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SOFTWARE DEVELOPMENT FOR THE AUTOMATIC CALCULATION OF DENTAL ARCH RELATIONSHIPS ON DIGITAL STUDY MODELS IN CLEFT LIP AND PALATE

A THESIS PRESENTED FOR THE DEGREE OF MASTER OF DENTAL SCIENCE

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TABLE OF CONTENTS – OUTLINE

TABLE OF CONTENTS - DETAIL

LIST OF FIGURES

LIST OF TABLES

ABBREVIATIONS

CAD	Computer aided design
CGH	Comparative genomic hybridisation
CL/P	Cleft lip and/ or palate
CL(P)	Cleft lip with or without cleft palate
CP	Cleft palate
CSAG	Clinical Standards Advisory Group
EDMA	Euclidean Distance Matrix Analysis
EMRs	Electronic Medical Health Records
FGFs	Fibroblast Growth Factors
GBD	Global Burden of Disease project
GPPA	Generalised Partial Procrustes Analysis
GWAS	Genome Wide Association Studies
IOTN	Index of Orthodontic Treatment Need
IPDTOC	International Perinatal Database of Typical Oral Clefts
MHB	Modified Huddart and Bodenham
NURBS	Non Uniform Rational B-splines
OFC	Orofacial clefting
Rhino plug-in	Rhinoceros, version 5 computer algorithm
SHH	Sonic Hedgehog Family

SNPs	Single-nucleotide polymorphisms
STL	Stereolithography
TGF-β	Transforming Growth Factor Beta Family
UCLP	Unilateral cleft lip and palate
WHO	World Health Organisation

LIST OF APPENDICES

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DECLARATION

I, Catherine Martin, declare that the following thesis is entirely my own work.

Signed:

Date: 20/1/16

ABSTRACT

Background: The assessment of dental arch relationships in the evaluation of surgical outcome in orofacial clefting is essential for quality assurance and optimisation of surgical protocols. Valid, reliable and standardised tools are required for multicentre comparison, evidence-based research and audit. Limitations with existing indices combined with emerging digital technology has led to a need for more contemporary, accurate and thorough measures of surgical outcome.

Objectives: To design, calibrate and validate an automated scoring tool for the assessment of surgical outcomes on digital models, using the modified Huddart and Bodenham (MHB) scoring system.

Design: Retrospective cohort of plaster and digital models from patients with unilateral cleft lip and palate.

Method: Design and development of an automated software tool took place prior to calibration of three examiners. Fifty-three digital and plaster study models were measured using conventional methods of MHB assessment. The MHB score was also measured using the automated software tool on digital models. The scoring was repeated twice one month apart and intra-observer reliability was calculated for each observer for conventional and automated

MHB scoring using intra-class correlation coefficients. Cronbach's alpha was used to calculate the inter-examiner agreement for scoring. Bland-Altman plots were used to demonstrate the level of agreement for each model medium.

Results: Intra-observer reliability was excellent for all examiners (0.988, 0.987 & 0.986). Overall agreement using Cronbach's Alpha for the three methods of scoring was also excellent (0.986). The automated software tool demonstrated the highest inter-observer reliability (0.991), followed by Plaster (0.989), followed by digital models using conventional MHB scoring (0.979). Bland-Altman plots confirmed no systemic bias and greater consistency of the scores with the automated software tool.

Conclusion: The study presents a valid, reliable and contemporary automatic scoring software tool for the assessment of dental arch relationships in orofacial clefting. The automated scoring tool has superior consistency and reproducibility to conventional methods of assessment using the MHB index.

CHAPTER ONE: INTRODUCTION

The global database on craniofacial anomalies indicates the overall incidence of orofacial clefting is approximately 1 in 700 live births, constituting one of the most common congenital deformities of the head and neck region (Mossey and Castillia, 2003). Clefting defects pose a significant functional and cosmetic burden on patients and families. Speech, hearing and cognition defects, poor social integration and higher morbidity are frequently identified in patients with clefts (Mossey et al., 2011). Surgical repair of the cleft restores both form and function, however overall care requires a multidisciplinary approach from birth until adulthood (Chuo et al., 2008).

Comparability within the UK regarding the incidence, treatment and outcome of orofacial clefting has significantly improved since the Clinical Standards Advisory Group (CSAG) investigation of cleft lip and palate services (Clinical Standards Advisory Group, 1998). However, treatment practices and protocols still exhibit large inter-center differences, resulting in variable outcomes for patients (Bearn et al., 2001). Therefore, clinical measures of outcomes are useful markers for quality assurance and enable multicentre comparisons.

One recurring difficulty with the assessment of outcomes is the standard to which it is examined and the availability of data. Where the validity and reproducibility of the outcome measures are questionable, the value of such research is downgraded and problematic for comparative investigations. In addition, there is tremendous difficulty in collating orofacial clefting information internationally, especially within the most deprived populations (Mossey, 2007). This is attributable to differences in measurements and classifications, combined with poor facilities and resources.

Research has been focused on overcoming the drawbacks of early classification systems in cleft care and progressing into the digital era. Studies investigating the reliability of scoring surgical outcomes on digital study models when compared to traditional study models in dental stone have shown promising results (Asquith and McIntyre, 2012, Asquith et al., 2007, Chalmers, 2015). However, automated approaches to scoring have not been previously investigated.

The focus of this research project is the development, calibration and validation of an automated system to evaluate outcomes in clefting defects for use on digital study models. As the clinical environment moves towards a 'paperless' method of working, the value of digital methods cannot be underestimated. The modified Huddart and Bodenham (MHB) scoring system (Mossey et al., 2003), that has been proven as a valid and reliable indicator for assessing surgical outcomes for patients with orofacial clefts (Gray and Mossey, 2005), will form the basis of this automated approach.

Development of a software tool to automate scoring of cleft lip and/ or palate surgical outcomes will ultimately increase the objectivity of assessment, which is limited with existing systems. The method of development for this software could be made available globally for use in all cleft organisations, supporting low resource centres lacking the crucial funds for software licences and analysis programmes. Such software would enable centres around the world to contribute outcome data to the Global Burden of Disease project (and other similar initiatives), which seek standardised data from countries with advanced care systems to those with limited access to care. Ultimately leading to a global estimate of residual morbidity following primary cleft repair.

CHAPTER TWO: LITERATURE REVIEW

2.1 Cleft Lip and/ or Palate

Clefting disorders, which may include cleft lip, cleft palate alone, or cleft lip and palate, constitute one of the most common congenital birth defects in humans. The word 'cleft' comes from an old English word meaning to 'split', which describes the classical appearance of these defects affecting the lips and oral cavity. When defining cleft lip with or without cleft palate CL(P) the following definitions should be referred to;

• "*Cleft lip with or without cleft palate: a congenital malformation characterised by partial or complete clefting of the upper lip, with or without clefting of the alveolar ridge or the hard palate. Excludes midline cleft of upper or lower lip and oblique facial fissure (going towards the eye)*" (Mastroiacovo et al., 2003).

• *"Cleft palate without cleft lip: a congenital malformation characterised by a closure defect of the hard and/or soft palate behind the foramen incisivum without cleft lip. Includes sub-mucous cleft palate. Excludes CL/P, cleft uvula, functional short palate, and high narrow palate"* (ICBDMS, 1991).

Cleft lip and/or palate (CL/P) can present as an isolated facial defect at birth, or associated with a wide spectrum of congenital syndromes. The CL/P defect is described according to the tissues involved and the side affected (Figure 1).

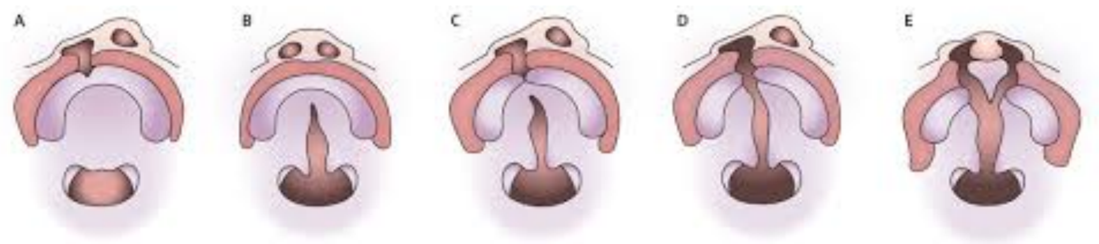

Figure 1: Orofacial Clefts (A) Cleft lip and alveolus (B) Cleft palate (C) Incomplete unilateral cleft lip and palate (D) Complete unilateral cleft lip and palate (E) Complete bilateral cleft lip and palate (Shaw, 1993).

2.2 Epidemiology

The incidence of CL/P is currently estimated to be approximately 1 in 700 live births (Mossey and Castillia, 2003). Data is collected from a variety of organisations and sources and summarised by the World Health Organisation (WHO) to obtain global figures for a defined period. This global register was last published in 2003 using data collected from 1993 to 1998 (Mossey and Castillia, 2003). Member registries for different geographical locations pertaining to their registered organisation, provide data for synthesis by the WHO.

More recent data, collected by the International Perinatal Database of Typical Oral Clefts (IPDTOC) over a 1 year period between 2000 and 2005, gives prevalence rates for all types of oral clefting (IPDTOC Working Group, 2011). The overall CL/P prevalence rate from a total of 7704 cases of CL/P was calculated to be 9.92 per 10,000. However, these data must be viewed with caution as over half of all registries invited to take part in the epidemiological study declined to participate.

UK epidemiological data for orofacial clefting indicates that unilateral cleft lip and palate (UCLP) and cleft palate (CP) account for the majority of the orofacial clefting phenotypes, while bilateral cleft lip and palate (BCLP), cleft lip (CL) and submucous clefts make up the remainder (McIntyre, 2014), (Figure 2).

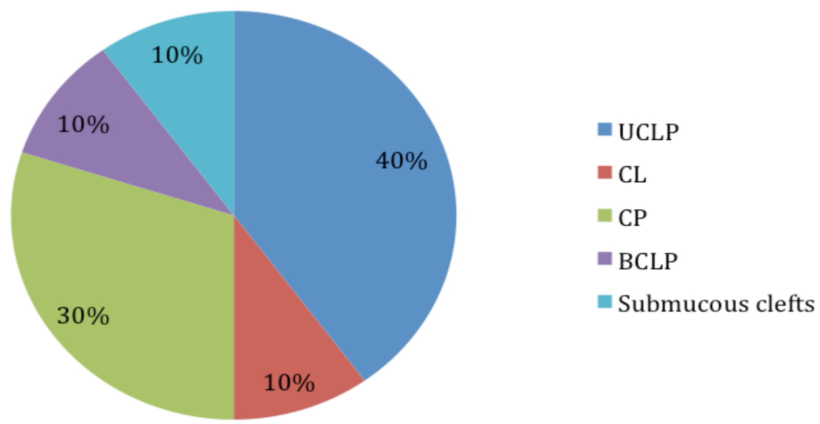

Figure 2: Pie chart displaying the relative proportions of different cleft phenotypes in the UK.

2.2.1 Cleft lip with or without a cleft palate [CL(P)]

Data from the WHO global register, suggests that CL(P) was highest in Bolivia followed by Tibet (Rosano and Mastroiacovo, 2001, Mossey and Little, 2002). The data also suggests Japan, the Philippines and South America have high prevalence rates. When collated, the prevalence for all types of orofacial clefting (isolated and associated with a syndrome) can be summarised for the following ethnicities:

Mongol > Caucasian > African

An overall mean prevalence rate has been recorded for isolated cleft lip with or without palate, at 7.9 per 10,000 births (range 3.4-22.9). Again a similar distribution was noted between geographical locations. Research indicates that whilst there is a distinct geographical distribution in prevalence rates, migrant populations display similar CL(P) rates to their country of origin (Mossey and Little, 2002).

2.2.2 Cleft Palate only

Cleft palate (CP) alone has an overall reported prevalence rate that is highest in Finish populations at 10.0-14.0 per 10,000 (Mossey and Castillia, 2003). Isolated, or syndromic cleft palate rates are calculated as a mean at 5.0 per 10,000 births, with a large range from 1.3 to 25.3 per 10,000 births (Mossey and Castillia, 2003). Countries with high rates of CP include Canada and Finland, while Cuba, Colombia and South Africa had comparatively low rates.

2.2.3 Clefting associated with a syndrome

Orofacial clefting (OFC) most commonly occurs in isolation, however there are approximately 6% of orofacial clefts associated with specific syndromes (Tolarová and Cervenka, 1998). Over 200 specific genetic syndromes have been identified to be associated with CL/P and over 400 with CP (Mossey et al., 2009). Seventy five percent of syndromic forms of orofacial clefts have been identified as the result of known environmental teratogens, chromosomal abnormalities or mutations in genetic loci (Leslie and Marazita, 2013). Van der Woude syndrome accounts for the most common form of syndromic CL/P and has been identified as a mutation of the gene encoding Interferon Regulatory Transcription Factor 6 (IFR6) (OMIM). IFR6 has a principle role in the development of Keratinocyte proliferation and differentiation. Successful genome wide sequencing has identified the mendelian inheritance at specific loci for many other gene variants.

2.2.4 Europe and the UK prevalence of clefting

European reported prevalence rates of CL/P are highest among countries in the north and lowest among those in the south of the continent (Mossey and Little, 2002) (Figure 3). Data indicates the overall prevalence rate for the British Isles is 9.25 per 10,000 (IPDTOC Working Group, 2011). Within Scotland, the overall prevalence rate for CL/P is approximately 1.4 per 1000 live births (Clark et al., 2003, Bellis and Wohlgemuth, 1999). Some CP rates are the highest in the world at 8.0 per 10,000 (Mossey and Castillia, 2003). Epidemiological surveillance in Europe for birth defects including CL/P is provided by the EUROCAT registry (www.eurocat-network.eu). This registry is funded by the European Union and is supported by the World Health Organisation's collaborating centre for congenital abnormalities. The National Health Service funds the CRANE database for England, Wales and Northern Ireland. This is responsible for registering births and demographic data on congenital abnormalities of CL/P. In Scotland the database is held by Cleft Care Scotland (CCS) Managed Clinical Network.

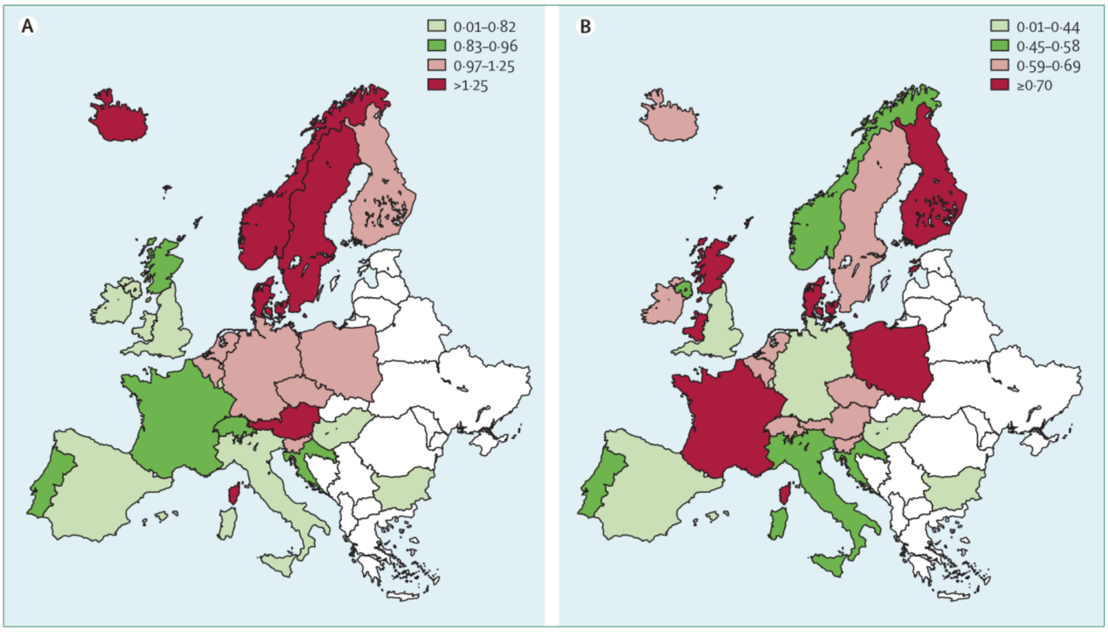

Figure 3: European birth prevalence per 1000 live births for (A) cleft lip with or without cleft palate and (B) isolated cleft palate. * Please note Scottish data for CL/P in this graph has been provided by EUROCAT, which differs slightly from the global data provided by Mossey and Castilla, 2003 and Clark et al, 2003.

2.2.5 International clefting prevalence

Deficiencies in the data exist for parts of the globe where resources are scarce and where birth surveillance systems are limited. These regions include Sub-Saharan Africa and India (Mossey and Modell, 2012). Available data suggests low prevalence rates exist for CL/P in such areas ranging from 0.3 to 1.65 per 1,000 live births (Mossey and Modell, 2012). The ascertainment of these data are questionable due to high numbers of infant mortalities in rural areas and other parts of the world such as Saudi Arabia, which suffer from a poor birth surveillance system despite having a high-income society. Prevalence rates are varied, however pooling of the data suggests the mean prevalence to be 1.25 per 1,000 live births (Mossey and Modell, 2012).

2.2.6 Sex distribution and laterality of clefting

The sex distribution of orofacial clefting is pooled from a smaller number of registries largely pertaining to the data available to the WHO. Of the 17 registries involved in this type of birth surveillance the male to female sex ratio for isolated CP was found to show a female predominance at 0.93, while data for CL/P shows a male sex ratio at 1.81 (Mossey and Castillia, 2003). These trends are also observed in the UK, with the CRANE database confirming a significant male predominance for CL, UCLP, BCLP (59.3%, 62.5% and 67.4%) and a higher female prevalence for CP (56.2%) (Fitzsimons et al., 2013).

Laterality data suggests the left side is consistently affected in unilateral orofacial clefts in all populations, in approximately 80-85% of individuals. (Fraser and Calnan, 1961, Paulozzi and Lary, 1999).

2.2.7 Limitations of global registers

Much of the information for descriptive epidemiology for CL/P is gathered through global registries. Birth prevalence data is lacking with reference to trends in seasonality, time and socioeconomic status. Difficulties with the assimilation of results from different registries pertain largely to the method of collection, differences in source population and inclusion and exclusion criteria (Mossey and Little, 2002). Furthermore, there are many parts of the world where data collection is challenging due to the high level of unreported birth rates in rural areas (Butali and Mossey, 2009), whilst infanticide in some cultures further distorts already poor quality epidemiological data.

2.3 Classification of clefting

Numerous classifications have been developed to aid the description, epidemiology and management of cleft subphenotypes. A few of the most notable classifications are outlined below:

2.3.1 Davis and Ritchie

An early system was proposed by Davis and Ritchie that broadly categorised a cleft according to the site within the alveolar process (Davis and Ritchie, 1922). Albeit simple, this classification has been criticised for not detailing the defect in relation to the primary and secondary palate, which is considered an important factor in cleft aetiology and pathogenesis (Smith et al., 1998).

2.3.2 Veau

This is a simple classification with 4 groups (Veau and Borel, 1931), however it fails to represent isolated cleft lip subtypes. Group I represents defects of the soft palate only, group II represents defects of the hard and soft palate involving the secondary palate only, group III represents unilateral defects from the soft palate to the alveolus and group IV represents complete bilateral clefts.

2.3.3 Kernahan and Stark classification and modifications

In 1958, Kernahan and Stark developed a system that could differentiate between some of the most commonly occurring cleft subtypes according to embryonic origin (Kernahan and Stark, 1958). They developed a 'Y' shaped schematic drawing (Figure 4), divided into 9 blocks that each represented an anatomical region. Shading the relevant box highlighted cleft involvement. Kernaham and investigators subsequently modified this system and this forms the basis of many systems still in use at present (Kernahan, 1971).

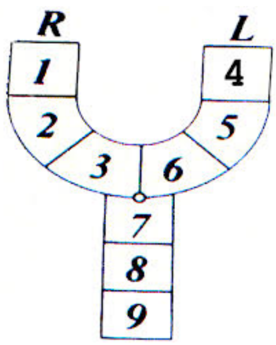

Figure 4: 'Y' shaped Kernahan and Stark classification for cleft subtypes.

This development was an improvement on the original classification system as it described the most usual forms of clefting. However, it has been criticised for the lack of detail particularly with reference to the degree of severity of lip, palate or asymmetric clefts (Smith et al., 1998). Therefore, the 'RPL system' was developed to significantly reduce complexity (Schwartz et al., 1993). Based on the modified 'Y' concept described by Kernahan it assigns one numerical digit for the three main anatomical regions. A total of 63 clefting defects can be represented in this way and the system itself to software analysis. Over-simplification of the system and limited visual representation however, limit the classification for routine use.

2.3.4 Friedman

A numerical model was developed that represented the depth of severity of the cleft (Friedman et al., 1991). It includes details on velopharnygeal valve function and defects of the nasal floor and arches, adding to the complexity of the system and introducing subjectivity.

2.3.5 Tessier

There are extended classification systems based on the appearances of the external facial cleft, to describe the cleft in terms of location such as the orbit and nasal cavities (Tessier, 1976). There are 14 categories.

2.3.6 ICD- 10

The WHO International Statistical Classification of Diseases and Related Health Problems 10th Revision is a standardised diagnostic tool for use across a variety of healthcare divisions to monitor global incidence and prevalence for a variety of diseases (World Health Organisation, 2015). Cleft subphenotyping is divided into three categories; CP (Q35), Cleft lip (Q36) and Cleft palate with cleft lip (Q37). Further subcategories are made for laterality and tissue involvement. It is regularly updated, however it has not gained widespread acceptance with researchers within the OFC field or other medical specialties as it has been criticised for being illogical, using terms that are both tautologous and inconsistent (Lewis, 1994, McBride, 2012).

2.3.7 LAHSAL

One of the most recognised and cited classifications is derived from Kernahan's 'Y' concept (Kriens, 1989). It is an alphabetic system with the acronym LAHSHAL. This describes 7 anatomical regions. These are the lip (left and right), alveolus (left and right), hard palate (left and right) and soft palate. The LAHSHAL letters represent each of these regions. In 2005, the Royal College of Surgeons recommended the omission of the second 'H' from the acronym, to become the LAHSAL system (Figure 5)(Hodgkinson et al., 2005). If the individual has a complete cleft this is recorded for the region with a capital letter. If a partial cleft is present only a lower case letter recorded. If a microform defect is present, this is represented with a lower case letter and parenthesis. Areas not affected are recorded with a dash.

For example, a complete cleft lip on the left side will be recorded as '**.....L**'. The system is compatible with software and is easy to use, whilst still representing a vast range of orofacial clefts.

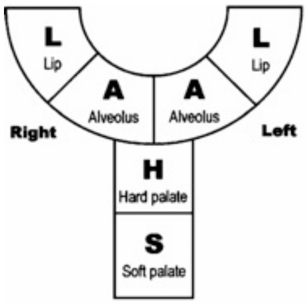

Figure 5: LAHSAL classification for cleft subtypes.

2.4 Pathogenesis of clefting

Development of the face begins during the third week post fertilisation when the first pharyngeal arch is formed. This is one of 6 arches that contribute to the physical appearance of the embryo. Each arch has 3 layers with a mesenchymal core, an outer ectodermal tissue layer and an inner endodermal tissue layer.

2.4.1 4th week

The first arch initially grows outward to form paired maxillary and mandibular processes. Dorsal to the maxillary processes is an expansive region of the forebrain known as the frontonasal prominence (Figure 6a). There is a small gap between the frontonasal prominence and mandibular process, known as the primitive oral cavity or stomodeum.

2.4.2 5th week

Ectodermal thickenings in the frontonasal prominence develop into nasal placodes. These are precursors to the olfactory epithelium. Further up-growth of surrounding frontonasal epithelium causes shallow depressions called nasal pits to develop. This divides the frontonasal prominence into paired medial and lateral nasal processes (Figure 6b). Nasal placodes are situated to the base of the nasal pits at this stage.

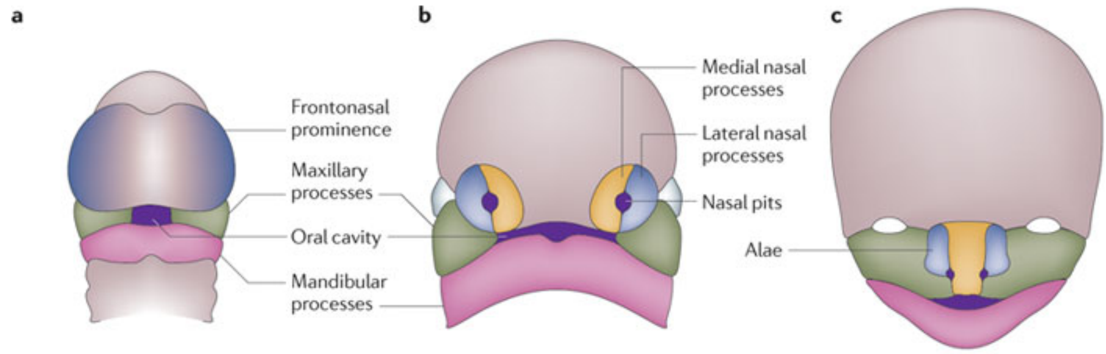

Figure 6: Image displaying the early stages of embryonic nose and lip development. (a) Fourth week in utero (b) Fifth week in utero (c) Sixth week in utero (Dixon et al., 2011).

2.4.3 6th week

Fusion of the medial processes with the maxillary processes forms the primary palate and upper lip (Figure 6c). Initially this fusion produces a thin strip of epithelial cells regarded as a 'nasal fin'. Subsequent breakdown and mesenchymal migration to form the intermaxillary segment and nasal alae develop. Failure of the nasal fin to disintegrate or epithelial cells to migrate, can lead to the presence of clefting of the lip (Jiang et al., 2006).

At the end of the 6th week, the development of the secondary palate occurs. Vertical outgrowths of the maxillary processes known as palatal shelves, form downwards adjacent to the developing tongue (Figure 7d).

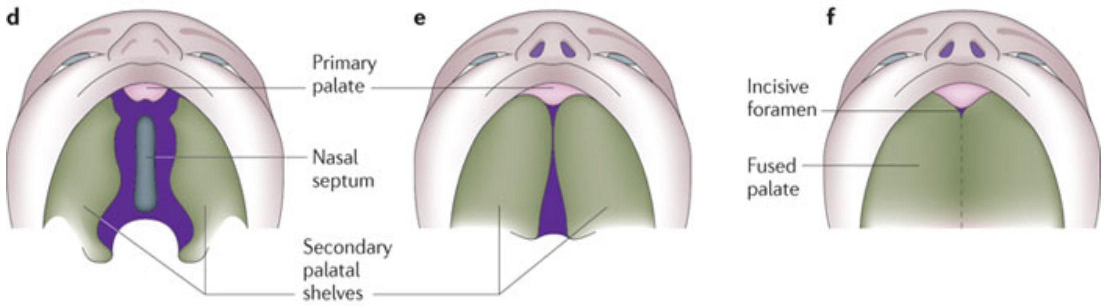

Figure 7: Image of palatogenesis in an embryo. (d) Elevation of palatal shelves. (e) Fusion of palatal shelves. (f) Fusion of primary and secondary palate (Dixon et al., 2011).

2.4.4 7th week

Co-ordinated cell signaling and hydration of the tissues mediated by hyaluronic acid, induces the maxillary shelves to ascend towards each other. The tongue simultaneously descends in the oral cavity. Fusion of the shelves requires assistance from glycoproteins and desmosomes, at an epithelial junction in a horizontal position above the primitive tongue. This is regarded as the secondary palate. Fusion occurs anteriorly in the hard palate region before zipping closed in a caudal direction for fusion of the soft palate (Figure 7e). Palatal rugae demarcate the regions between the anterior and posterior regions of the palate. This divides the oro-nasal cavity to facilitate respiration and mastication to occur in their respective nasal and oral cavities.

It has been suggested that the undifferentiated epithelial junction at the line of fusion undergoes transformation through cell migration and differentiation to a uniform un-arched mesenchymal palate (Sperber et al., 2001). However, controversy exists as to whether it is merely co-ordinated through epithelial migration and apoptosis (Xu et al., 2006).

2.4.5 9th week

Anteriorly, the secondary palate fuses with the primary palate and nasal septum, which is complete by the 10th week (Figure 7f). Anterior and lateral shelf elevation and fusion is demarcated by the incisive foramen.

2.4.6 Dysmorphic development

Disruption in the complex interplay of cells during embryogenesis is the primary cause for abnormalities in CL/P. During normal palatogensis, cells in the epithelial seam migrate laterally towards the mesenchyme with sections of the basal lamina. In addition, cells in this region reduce in thickness to form a thin juncture at the site of fusion. This is a co-coordinated pathway mediated through cell migration and differentiation, apoptosis and growth (Berkovitz et al., 2009). The exact signaling role is not clear, but failure of epithelial apoptosis or migration after early fusion has been linked to breakdown of the epithelial seam (Dudas et al., 2007).

2.5 Aetiology of CL/P

The primary and secondary palate are of separate genetic and embryological origins (Fraser, 1954, Fogh-Andersen, 1942), and this gives rise to variation in CL/P phenotypes. Research has confirmed that CL/P exhibit segregant genotypes and these are key in the comprehension of craniofacial morphogenesis. This has been achieved through familial human studies, genome-wide association studies (GWAS), linkage analysis and animal experiments on mice and chicks. The precise aetiology is largely unknown regarding cleft defects, however there is unanimous agreement that a complex interaction between genetic and environmental factors leads to this disruption of facial morphogenesis (Abu-Hussein, 2012).

2.6 Genetic factors

Epidemiological studies within families, monozygotic and dizygotic twins have provided evidence for strong population heritability of non-syndromic OFC. The search for the precise genetic factors has involved linkage and association studies, animal models, cytogenetics and more recently genome wide association techniques. The first publication from the Human Genome Project estimated the number of total protein coding genes to be approximately 20,000 to 25,000, with two thirds of these genes implicated in the development of the craniofacial region and syndromic conditions with CL/P as part of the phenotype (Consortium, 2004). The latest estimate is a more conservative figure for the human genome with 19,000 protein coding genes and 2,000 non coding genes (Ezkurdia et al., 2013). *FaceBase* is an online consortium that has been established for recording and co-ordinating the research in gene expression during aberrant embryonic craniofacial development, identifying genes linked to syndromic and non-syndromic CLP phenotypes (Table 1).

Table 1: A selection of genes that are known to contribute to syndromic and non-syndromic CLP Phenotyes (Sperber and Sperber, 2013).

Gene	Gene/protein	OMIM	Associated syndrome (OMIM)/functional role	Location
ALX3	Aristaless-like homeobox 3	606014	Frontonasal dysplasia type 1 (136760)	1p13.3
ARHGAP29/PARG1	Rho GTPase-activating protein	610496	Candidate gene associated with nonsyndromic CL/P	1p22.1
BMP4	Bone morphogenetic protein 4	112262	Orofacial cleft 11 (600625)	14q22-q23
CLPTM1	Cleft lip and palate transmembrane protein 1	604783	t(2;19)(q11.2;q13.3) translocation described in three-generation pedigree with nonsyndrome CL/CP	19q13
CRISPLD2	Cysteine-rich secretory protein LCCL domain containing 2	612434	Candidate gene associated with cleft lip/palate	16q24.1
DLX5	Distal-less homeobox 5	600028	Proximodistal patterning of the pharyngeal arches; oronasal patterning	7q21.3
EFNB1	EPH-related receptor tyrosine kinase ligand 2	300035	Craniofrontonasal dysplasia (304110)	Xq13.1
FAF	FAS-associated factor 1	604460	Pierre Robin sequence, cleft palate only	1p32.3
FGF8	Fibroblast growth factor 8	600483	Kallmann syndrome 6 (612702); cleft lip/palate	10q24
FGF10	Fibroblast growth factor receptor 10	602115	Aplasia of lacrimal and salivary glands (180920); lacrimoauriculodentodigital syndrome (LADD; 149730)	5p13-p12
FGFR1	Fibroblast growth factor receptor 1	136350	Pfeiffer syndrome (101600), Kallmann syndrome type 2 (147950)	8p11.23-p11.22
FGFR2	Fibroblast growth factor receptor 2	176943	Apert syndrome (101200), Pfeiffer syndrome (101600); craniosynostosis and midfacial hypoplasia syndromes; LADD syndrome (149730)	10q26.13
FOXE1 (TTF-2)	Forkhead homolog-like 15/thyroid transcription factor 2	602617	Bamforth-Lazarus syndrome (241850)	9q22.33
GLI2	GLI-Kruppel family member 2	165230	Holoprosencephaly type 9 (610829), cleft lip and palate	2q14.2
GSC	Goosecoid	138890	Homozygous knockout mouse model exhibits aplastic nasal apparatus	14q32.1
GSCL	Goosecoid-like	601845	Located in the DiGeorge syndrome deletion region	22q11.21
HOXA1	Homeobox A1	142955	Athabaskan brainstem dysgenesis (601536); Bosley-Salih-Alorainy syndrome (601536)	7p15.3
IRF6	Interferon regulatory factor 6	607199	Van der Woude syndrome type 1 (119300); popliteal pterygium syndrome (119500); oralfacial cleft 6 (IRF6 enhancer; 608864)	1q32.3-q41
JAG2	Jagged2	602570	Alagille syndrome; association with cleft palate	14q32
LHX6	Lim homeobox protein 6	608215	Expressed in palatogenesis	9q33.2
LHX8	Lim homeobox gene 8	604425	Associated with cleft lip	1p31.1
MEOX2	Mesenchyme homeobox 2	600535	Posterior palate expression in mouse models	7p21.2
MIR140	MicroRNA 140	611894	Regulates *PDGFA* expression; cleft palate	16q22.1
MSX1	Muscle segment homeobox 1	142983	Oralfacial cleft type 5 (608874); tooth agenesis (106600); Witkop syndrome (189500)	4p16.2

Note: Online Mendelian Inheritance in Man (OMIM) number is represented in the online database of human genes and genetic disorders. This can be accessed at http://www.omim.org/

Table 1. A selection of genes that are known to contribute to syndromic and non-syndromic CLP phentotypes (Sperber and Sperber, 2013).

MSX2	Muscle segment homeobox 2	123101	Craniosynostosis type 2; enlarged parietal foramina (168500)	5q35.2
OFC1	Unknown	119530	Oralfacial cleft type 1 (119530)	6p24.3
ORS2	Odd-skipped related 2	611297	Cleft palate in knockout mouse	8q22.2
OTX2	Orthodenticle homolog 2	600037	Anophthalmia, micro-ophthalmia (610125)	14q22.3
PAX7	Paired box homeobox gene 7	167410	Neural crest specification; possible influence on CL/P risk	1p36.13
PDGFC	Platelet-derived growth factor C	608452	Mitogen, associated with CLP	4q32.1
PLCB4	Phospholipase C, beta-4	600810	Auriculocondylar syndrome (602483)	20p12
PTCH1	Patched 1	601309	Holoprosencephaly type 7 (610828), basal cell carcinoma (605462), CLP	9q22.32
PVRL1	Poliovirus receptor-like 1/NECTIN-1	600644	Cleft lip/palate-ectodermal dysplasia syndrome/Zlotogora-Ogur/Margarita Island syndrome (orofacial cleft 7; 225060)	11q23.3
RUNX2	Runt-related transcription factor 2	600211	Cleidocranial dysplasia (119600); implicated in CLP	6p21.1
RYK1	Receptor-like tyrosine kinase	600524	Implicated in oral cleft studies	3q22.1
SATB2	Special AT-rich binding protein 2	608148	Implicated in orofacial clefting	2q33.1
SHH	Sonic hedgehog	600725	Holoprosencephaly type 3 (142945)	7q36
SPRY2	Sprouty homolog 2	602466	Candidate gene for nonsyndromic cleft lip and palate	13q31.1
SUMO1	SMT3 suppressor of mif two 3 homolog 1	601912	Oral facial cleft type 10 (601912)	2q33.1
TCOF1	TREACLE	606847	Treacher Collins-Franceschetti syndrome I (154500)	5q32.q33.1
TBX22	T-box 22	300307	X-linked cleft palate with ankyloglossia (303400)	Xq21.1
TBX10	T-BOX 10	604648	Associated with cleft lip with or without cleft palate	11q13.2
TFAP2A	Transcription factor AP-2 alpha	107580	Branchio-oculo-facial syndrome (113620)	6p24.3
TGFB3	Transforming growth factor beta 3	190230	Cleft palate in mouse model	14q24.3
TGFBR1	Transforming growth factor, beta receptor I	190181	Loeys-Dietz syndrome type 2A (608967), cleft palate	9q22.33
TGFBR2	Transforming growth factor, beta receptor II	190182	Loeys-Dietz syndrome type 2B (610380), cleft palate	3p24.1
TP63	Tumor protein p63	603273	Ectrodactyly, ectodermal dysplasia, and cleft lip/palate syndrome 3 (604292); OFC8 (129400)	3q28
WDR65	WD-repeat domain 65;	614259	Van der Woude syndrome type 2 (606713)	1q34.2
YPEL1	Yippee-like 1	608082	Located in the commonly deleted DiGeorge (188400)/velocardiofacial (192430) region	22q.11.2

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There are a large number of syndromes related to CL/P (Table 1), with the knowledge of syndromic clefting being more complete than for non-syndromic clefting. This is because there is a clear gene regulatory control network that underpins facial morphogenesis and this can be linked to specific phenotypic features in the identification of syndromes. However, the exact role of each gene in morphogenetic patterning of CL/P is not fully understood and the identification of a gene only provides a small insight into the dysmorphic development in clefting due to the interplay of environmental factors.

2.6.1 Hedgehog gene family

Desert, Indian and Sonic Hedgehog morphogenes have all been identified with a significant role in craniofacial development (Pan et al., 2013). Sonic Hedgehog (SHH) is a particularly important morphogene for the development of the frontonasal and maxillary processes. Over-expression of this signaling molecule has led to increased mediolateral expansion of the midface (hypertelorism), while loss of SHH function can lead to orofacial clefting (Hu and Helms, 1999). The cell interaction is mediated with a number of other morphogenes such as the Transforming Growth Factor Beta family (TGF-β). This superfamily of cytokines includes Bone Morphogenic Proteins (BMPs), which are responsible for apoptosis, cell differentiation and proliferation (Dudas and Kaartinen, 2005). More specifically TGF-β has a role in medial edge epithelial cell migration during palatal shelf fusion.

2.6.2 Homeobox gene family

Homeobox genes such as MSX1, encode a transcription repressor protein with a role in cell proliferation in the anterior part of the secondary palate. Disruption of this gene leads to the development of CL/P in non-syndromic individuals (Jezewski et al., 2003), while loss of SHOX2 results in clefting of the anterior hard palate. This indicates the genetically independent fusions of the posterior and anterior palates (Yu et al., 2005).

2.6.3 Other gene families

Fibroblast growth factor (FGFs) genes are expressed in the anterior region of the palate during palatal shelf fusion, and combined with the signaling effects of BMP can regulate SHH expression (Chai and Maxson, 2006). Other morphogenes found to be involved in the regulation of embryogenesis are OSR2, PAX9, endothelin, platelet derived growth factor, and the WNT signaling family. Animal models have enabled categorisation of gene defects into five discrete developmental stages that may lead to clefting of the palate (Chai and Maxson, 2006). These are as follows:

1) Failure of palatal shelf formation (FGFR2, activin-β)

2) Fusion of the palatal shelf with the tongue or mandible (FGF10, TBX22)

3) Failure of palatal shelf elevation (PAX9, OSR2)

4) Failure of palatal shelves to meet after elevation (MSX1, SHH)

5) Persistence of medial edge epithelium (TGFB3, TGF-β3)

Genetic control of lip development is tightly regulated through a similar set of signaling molecules as for palate formation (Jiang et al., 2006). However, failure to induce apoptosis or epithelial-mesenchymal transformation in the cells at the approximated edges of the mesial nasal processes, is a different genetic dysfunction rather than a 'fusion' defect that could be described in clefting of the palate (Jiang et al., 2006). While there has been an influx of new research evidence for the genetic regulation and dysregulation during embryogenesis, the precise interaction of signaling molecules and cell interactions is unclear.

2.6.4 Cytogenetics and array Comparative Genomic Hybridisation

Cytogenetic studies is of prime importance for analysing the structure of human and animal chromosomes, and isolating responsible genes in the aetiopathogenesis of OFC (Singh et al., 2012). Array Comparative Genomic Hybridisation (CGH) is a technique used in cytogenetics that specifically identifies the structural variation in DNA sections of the genome in DNA test samples against reference samples. Within OFC it is used to effectively compare DNA samples in family members where the genome is likely to be closely related, to ascertain differences in the chromosomal ploidy level (Rahimov et al., 2012). CGH use is a valuable technique for positional localisation of candidate genes for OFC on the human genome, however more research is required to optimise its potential in genetic localisation and identification through microdeletions and copy number variation.

2.6.5 Genome Wide Association Studies

GWAS studies have enabled substantial progress in mapping genes for OFC research, especially non-syndromic CL/P (Dixon et al., 2011). It facilitates the cross-matching of genome sequences from cases and controls, with a specific focus on single-nucleotide polymorphisms (SNPs) to isolate common risk alleles. Statistical modeling has now enabled GWAS to help determine the risks for gene–environment interactions, with higher risks associated with maternal smoking and alcohol consumption during the peri-conceptual period, and lower risks with multivitamin supplementation (Beaty et al., 2011). The main drawback to GWAS is its ability to identify relatively common, low penetrance polymorphisms. In addition, large sample sizes are needed to show relatively small increases in risk ratios for genetic loci isolated in non-syndromic CL/P (Rahimov et al., 2012).

2.6.6 Consanguinity

Consanguineous marriages between first and second cousins, is widely practiced among many populations in the Middle East, West Asia, South India and North Africa. It is thought these marriages offer greater long term stability by a greater likelihood of partner compatibility (Hamamy, 2012). However, the offspring of such unions are at greater risk of inheriting autosomal recessive mutations (Hamamy, 2012). The familial risk of CL/P to individuals with first degree relatives has been estimated to be 32 fold for cleft lip and 56 fold for CP (Sivertsen et al., 2008). In a population based study in Saudi Arabia (a population with a high number of consanguineous marriages), prevalence of non-syndromic orofacial clefting in consanguineous marriages is reported to be as high as 57% (Alamoudi et al., 2014). Therefore, preconception and premarital genetic counseling should be considered a priority for such communities (Hamamy, 2012), and in the context of OFC, for those couples where there is a family history of OFC.

2.7 Environmental factors

The complex interaction between genetic and environmental factors in CL/P has made research in this field challenging. A systematic review has suggested there is a strong connection between tobacco smoking, maternal alcohol consumption, folic acid intake as a protective factor, poor nutrition, stressful events, low blood levels of zinc and febrile illness during pregnancy (Molina-Solana et al., 2013).

2.7.1 Smoking, alcohol and social deprivation

Maternal smoking has been extensively investigated with large numbers of case-control and cohort studies suggesting a modest dose-response effect (Little et al., 2004). It is only recently that data is beginning to be examined for the evidence of passive smoking as a link to orofacial clefting (Li et al., 2010). The effect of maternal alcohol consumption in the aetiology of CL/P is controversial, despite its accepted link to foetal alcohol syndrome (Mossey et al., 2011). This correlates with evidence to support the socio-economic status and prevalence of orofacial clefting. One large notable study carried out in Greater Glasgow between 1974-1985 demonstrated high rates of social deprivation and unemployment to be linked to the highest rates of orofacial clefting while affluent areas to have the lowest (Womersley and Stone, 1987). Although this has been reflected in several studies since 1987, caution has been advised when interpreting data due to differences in recording socio-economic status, confounding factors and population stratification (Mossey et al., 2011).

2.7.2 Nutrition

Obesity (Blomberg and Källén, 2010), poor Vitamin B-6 status (Little et al., 2004), and low levels of zinc in maternal blood samples (Tamura et al., 2005) have all been found to have a positive correlation to clefting defects. The link between obesity and clefting is unclear and presents as a small risk, however with the incidence of obesity rising in developed countries this could be significant (Izedonmwen et al., 2015). Research investigating the protective effect of folic acid in the prevention of OFC in embryogensis is inconsistent (Mossey et al., 2011). The current evidence is based on epidemiological studies in countries that have introduced compulsory fortification of grain with folic acid, along with large case-control studies. Data appears to be controversial regarding folic acid through dietary fortification with protective roles afforded in North America, while not in Chile or Canada (Mossey et al., 2011). However, a meta-analysis has recently concluded that folic acid multivitamin supplementation maybe beneficial for reducing the overall CL/P incidence (Molina-Solana et al., 2013).

2.7.3 Lifestyle factors

Teratogens both at home and in the workplace may have a link with CL/P. Febrile illness during pregnancy, exposure to air pollutants and organic solvents, riboflavin, Vitamin A, retinoids, and corticosteroids may contribute to an increased risk of clefting (Mossey et al., 2011). Anti-convulsant medications have been found to be a risk factor for developing orofacial clefting such as phenytion (Puhó et al., 2007), phenobarbital (Arpino et al., 2000) and benzodiazepines (Enato et al., 2011). Further high quality research is needed to investigate the precise role of each environmental risk factor whilst excluding potential confounding factors.

2.8 Genetic and environmental interaction

Comprehension of the interaction between environmental and genetic factors is important for the accurate understanding of aetiological factors and prevention strategies by public health authorities (Mossey et al., 2009). Maternal smoking has been linked with genetic variants in IRF6 (Wu et al., 2010), and genetic modifiers of the detoxification pathways GSTT1 (Shi et al., 2007), suggesting underlying susceptibility to OFC (Dixon et al., 2011). Polymorphisms affecting ADH1C haplotype alcohol dehydrogenase gene leading to reduced alcohol metabolism has been shown to increase the risk of OFC in the offspring of mothers who heavily consume alcohol during early pregnancy (Boyles et al., 2010). Many other genetic/environmental effects have been studied and a meta analysis has been proposed by the WHO to analyse the results of these studies (Mossey et al., 2009). This would give weighting to prevention strategies targeting avoidance to environmental teratogens, genetic counseling and vitamin supplementation (Mossey et al., 2011).

2.8.1 Epigenetics

Epigenetics can be defined as 'a group of acquired or inherited and potentially transgenerational dynamic molecular mechanisms that are affected by the environment and act directly upon the genome and genetic machinery throughout life to regulate gene expression' (Williams et al., 2014). Gene expression and phenotype are subsequently altered at a molecular level by such environmental factors (Feil and Fraga, 2012). Research in this field will undoubtedly contribute to long term preventative advice (Williams et al., 2014).

2.9 Management

The management postpartum for patients born with CL/P and their parents is both long and arduous and involves a multidisciplinary approach. The health problems faced by patients with CL/P includes; feeding, speech, hearing, psychological, dental, disruption to normal growth and development, and increased morbidity due to treatment (Vasanth et al., 2013). Therefore, teams involved in CL/P care are: Maxillofacial and Plastic surgeons, ENT specialists, Paediatricians, Orthodontists, General Dental Practitioners, Psychologists, Speech and Language therapists, Audiologists, Specialist Nurses, Nutritionists with potentially many other specialties particularly in syndrome associated CL/P. The management of children and adults with clefts will be described in relation to chronological age.

2.9.1 Diagnosis

A diagnosis of an orofacial abnormality is detected through coronal and frontal planes of the developing fetus. Deviations from the mid facial axis or protruding soft tissue masses give rise to further investigation with a full anatomical survey

(Berkowitz, 2006). Despite this, the sensitivity of ultrasound is low, particularly for CP, where detection varies with operator experience, equipment and gestational age at the time of ultrasound. Nonetheless, it is valuable in early diagnosis to enable early counseling and referral to appropriate services. Early psychological management begins from the time of diagnosis for the parents, with early input being beneficial to develop emotional support and coping strategies.

Technological advancement in sonography has enabled higher detection rates with improved specificity and sensitivity. Through this, Scottish detection rates have improved between 1999 to 2008 (Paterson et al., 2011). A diagnosis of CL/P can be made at 12 weeks in utero (Berge et al., 2001) although this is not 100% accurate due to factors including positioning of the embryo, maternal obesity and scanning technique.

2.9.2 0 - 3 months

In the UK, when a patient is born with CL/P, specialist teams are contacted to visit the parents and patients within the first 48 hours. They offer advice on feeding, airway management along with explanations for the parents and psychological input. Support is also provided by volunteer members of the Cleft Lip and Palate Association (CLAPA), a UK based charity. Most babies also have an auditory brainstem response test carried out to determine if a sensioneural hearing defect is present.

2.9.3 3 – 12 months

Lip repair of the cleft is usually performed at 3-12 months of age. This restores form and function and is commonly achieved with the Millard rotation advancement flap (Millard Jr, 1964). Re-apposition of the muscles, mucosa and skin are achieved. Surgeons aim to leave the scarring running concurrently with the philtrum of the lip. There is wide variation in the precise details of the procedural technique between individual surgeons. Feeding management usually continues with the baby being weaned as per non-cleft protocols. Early speech development is encouraged at 'babble' groups.

2.9.4 12 months – 3 years

At 12 to 18 months palate repair divides the oro-nasal cavities to facilitate normal velopharyngeal function. Controversy exists regarding the optimal time for palate repair, and a balance must be struck between early closure for normal speech development and restrictions in normal maxillary growth from scar tissue. Vomer flaps, that utilise the mucoperiosteal tissue around the vomer bones of the nasal septum, and oral mucoperiosteal flaps are commonly used to achieve repair (Madahar et al., 2013).

Inadequate palatal closure can disrupt the function of the eustachian tube leading to recurrent otitis media. If an effusion is also present 'glue ear' is diagnosed. The subsequent management may lead to the insertion of grommets placed under general anaesthesia. Speech development will be affected unless prompt management is taken (National Institute for Health and Care Excellence, 2008). Where complete union of the hard or soft palate has not been achieved a palatal fistulae persists. This can lead to air escape from the oral to nasal cavities leading to hypo-nasality and velopharyngeal insufficiency. Repair can be achieved with a nasendoscopy or a pharyngoplasty technique usually at pre-school age. Speech and Language Therapists, Audiologist and ENT surgeons will play an integral role in this part of a child's development.

2.9.5 3 – 5 years

Lip revision is often considered at this stage where necessary. Routine examination by the dental profession is commenced, either in primary or secondary care. Unfortunately a high proportion of CL/P children are found to have caries (Bearn et al., 2001). It has been suggested as a result of frequent high sugar rewards for attending hospital appointments, a lack of tooth-brushing where surgical sites are sore and anxiety to brush cleft sites (Vasanth et al., 2013). The Department of Health has issued an oral prevention toolkit to guide dental healthcare providers in the management of patients with a high caries risk, such as patients with CL/P (Public Health England, 2014). Other dental anomalies often found in patients with CL/P include supernumeraries, hypodontia, malformed teeth, ectopia, crossbites, crowding and delayed eruption of teeth.

2.9.6 5 years – adolescence

At the age of 8 to 9 years orthodontic intervention for children with an alveolar cleft may begin with expansion of the maxilla using a quadhelix or rapid maxillary expansion device. This will correct posterior crossbites and achieve access for surgeons during bone grafting, usually at around 10 years of age. Teeth that are sited within the cleft defect are often extracted prior to bone grafting to improve bony healing. Bone is often harvested from the iliac crest, however synthetic alternatives are under investigation. This includes Beta-Tricalcium Phosphate and anorganic bovine bone (De Ruiter et al., 2015, Tuo, 2008). Intervention at this stage is aimed at providing bone in the cleft region to allow for spontaneous eruption of the permanent canine, and support for the alar base of the nose. Repair of a fistula can often be undertaken at the same time as bone grafting.

2.9.7 Adolescence - adulthood

At the age of 12-14 years definitive orthodontic treatment is carried out. For most patients this involves fixed appliances and extractions with tooth quality issues and hypodontia dictating the extraction pattern in many cases. In a few cases where a Class II malocclusion is present, a functional appliance maybe indicated. Facial growth is determined at the age of 17 years when Orthognathic surgery may be required. A class III skeletal component is common from a restriction of maxillary growth due to scar tissue and severe malocclusions may warrant the use of distraction osteogensesis. This applies a force to osteotomised bone ends to achieve greater movements than can be achieved with conventional surgery alone. Services from specialists in restorative dentistry are frequently involved and dental implants have been shown to have high success rates in patients with CL/P. They should be placed after growth has ceased and 4 to 6 months post-bone grafting (Wermker et al., 2013).

The treatment of adult patients with clefting is assessed and managed on an individual basis. Lifelong support is provided by the cleft services within the UK. Adult patients who may not have received comprehensive surgical care during childhood, are often managed with obturators to seal off the oral and nasal cavities or removable palatal lift appliances to aid speech.

2.9.8 Cleft Care Scotland (CCS) management pathway

The latest report issued by CCS indicates the network manages 1,152 patients with clefts of varying phenotype (Gallacher, 2012/13). Eighty individuals were born in Scotland with orofacial clefts between 2012 and 2013, with a particularly high percentage of CP, consistent with previous years. Network co-ordinators have agreed pathways for the management of patients within the CCS network (Appendix I). The managed clinical network travels out to local centers as a whole unit to provide access to treatments for patients. This reduces the overall burden of care for individuals and their families as it has a high number of patients in rural geographical locations. This is different from the hub and spoke type service that exists within England and Wales.

2.9.9 Timing for surgical repair

Surgical repair of a cleft defect in children can have deleterious effects on growth of the maxilla (Friede and Enemark, 2001, Holland et al., 2007, Noverraz et al., 1993, Witzel et al., 1984). Graber first established that a disruption to the palatal structures resulted in unfavourable growth of the midface (Graber, 1949). He questioned surgeons who were operating at an early age to close palatal clefts. It quickly became the debate among cleft teams over the ideal time to operate. Bishara and his co-workers published their findings in the 1970's showing that patients with untreated clefts of the lip, palate and alveolus demonstrated reasonably normal midfacial growth (Bishara et al., 1979, Bishara et al., 1985, Bishara et al., 1976). Late or delayed closure (time of the mixed dentition) with a two stage approach, has been demonstrated to produce more favourable outcomes for patients with orofacial clefting (Friede and Enemark, 2001).

However, the consequences of delayed palate closure in patients with CL/P can have negative effects on overall outcomes for speech, function and aesthetics (Witzel et al., 1984). Timing of the procedure and surgical method are therefore essential determinants of future treatment, management and ultimately outcome. Despite many years of research in cleft care, the controversy regarding when to surgically intervene has yet to be definitively resolved. Cleft units are therefore currently using treatment protocols based on a mixture of evidence, operator opinion and expertise.

2.9.10 Audit

Throughout multidisciplinary care from birth to adulthood in Scotland, records are collected and uploaded to the Cleft Care Scotland National Clinical Audit System (NCAS) for audit and research purposes. They are a mandatory component of patient care and are essential to establish and optimise patient outcomes. Records are collected at 5, 10, 15 and 20 years and include study models, radiographs, photographs, audiograms, typanometry, otoscopy, dental health assessments, surgical audit data and orthodontic audit forms.

2.10 Improvements in cleft services

In the late 1980's cleft care came under scrutiny from a growing body of professionals who felt care in the UK was falling short of the acceptable standards. It prompted several comparative studies and development of scoring systems for assessing outcomes for patients with CL/P.

2.10.1 Six centre international study

A six centre Northern European comparative study of 9 year old orthodontic records investigated nasiolabial appearance, dental arch relationships, and craniofacial form in UCLP patients (Asher-McDade et al., 1992, Shaw et al., 1992, Mølsted et al., 1992). Results were tentative and subjective owing to differing expectations of the cleft centres and a lack of standardisation (Shaw et al., 1992). Successful outcomes were associated with the use of vomer flaps for surgical intervention of anterior palate closure while poor outcomes were found with active presurgical orthopedics (Shaw et al., 1992). It opened the field for further research and improvements in study design.

2.10.2 Eurocleft Study

A longitudinal cohort study, built on the findings of the six-centre international comparative study, became known as the Eurocleft study (Brattström et al., 2005). It provided information on patient and parent satisfaction, the impact of treatment on quality of life, and the inter-relationship with treatment outcome (Brattström et al., 2005, Mølsted et al., 2005, Semb et al., 2005). It was hoped this would provide more valuable feedback to the centres involved and act as a marker of quality in cleft care services. Results indicated dissatisfaction from patients regarding a range of treatment aspects.

Emphasis was placed on the large variation in treatment protocols between centres and the amount of treatment received. Centres with the most demanding protocols and intense treatment regimes performed poorly when looking at patient outcome (Shaw et al., 2005). This was particularly evident for the UK centres and promptly led to the CSAG investigation.

2.10.3 Clinical Standards Advisory Group

CSAG was established by UK Health Ministers 'to advise on the access and availability of selected NHS specialist services'. Its principle aim was to prevent specialist care falling to a standard that was unacceptable and undetectable. A working group was established to assess the quality of care in the UK for children aged 5 and 12 years born with UCLP (Sandy et al., 2001). A secondary aim was to highlight the training of the health care professionals providing the care for these particular patients.

In a series of journal articles the results were not encouraging with regards to the current standards of care (Sandy et al., 2001, Bearn et al., 2001, Sell et al., 2009). Poor outcomes were found for dental arch relationships (many likely to require orthognathic surgery), bone graft procedures, speech and high caries rates. Operator volume was low and clinicians had received little structured training particularly for procedures that were carried out on a daily basis (Bearn et al., 2001).

Comparisons with the data from the Eurocleft Study highlighted the quality of care in the UK was trailing behind European counterparts. (Brattström et al., 2005, Mølsted et al., 2005, Semb et al., 2005, Shaw et al., 2005). The CSAG committee made a number of key recommendations to the UK government to initiate change. Recommendations included reducing the number of centres in the UK, setting up a national registry database and robust training pathways for cleft care providers.

Restructuring cleft services and the allocation of funds was completed with the help of the Cleft Implementation Group, reducing the number of centres to 15. The follow on investigation into cleft care in the UK is now complete with a second published report investigating the impact of reorganisation of cleft services expected imminently. Results are expected to show larger operator volume for cleft surgery associated with more successful outcomes. However, disappointing preliminary findings are that speech outcomes and untreated caries levels have not improved (Sandy, 2015).

2.10.4 The Eurocleft Project 1996-2000

At the same time as the CSAG study was commissioned, the European commission began its project to establish cleft network centres across the European Union leading to improved standards of cleft care (Shaw et al., 2000).

Members of the steering group nominated candidates from each country to represent their respective cleft centre. This formalised a network. Evaluation of cleft services was achieved through questionnaires from 201 cleft centres from 30 European countries. Results of the project indicated that standards of cleft care had suffered as a result of haphazard development and limited guidance. There were many different protocols and procedures taking place within the centres, many of which failed to be based on sound evidence. A handful of centres were operating well below the minimum number of cases suggested per annum to achieve optimal clinical care and experience. Similar findings were emerging from the UK CSAG report. Local constraints and personalities appeared to be particularly reluctant to implement new guidelines or evidence based medicine for fear of damaging personal reputation or pride.

The Eurocleft project was key in establishing areas for future research and audit. The *Eurocleft Consensus recommendations* that have undoubtedly helped achieve improved standards of cleft care globally, both at a local level and from a governmental and organisational approach (Shaw et al., 2000).

2.10.5 EUROCRAN

This European project commenced in 2000 functioning as an international research consortium. Funded by the European Union, it had five main domains to improve the management of individuals born with craniofacial anomalies (Shaw, 2004b). These domains included; molecular diagnostics, genetic sequencing and identification, research of surgical techniques, gene-environment interaction studies, and an online European Craniofacial Directory (www.eurocran.org) in connection with a Good Practice Reference Archive. EUROCAT is now the online European registry for birth surveillance of CL/P.

2.10.6 EUROCleftNet

This is a network for orofacial cleft research, prevention and treatment (www.eurocleftnet.org). It is funded by the European Science Foundation and has primary objectives in improving patient-focused research collaboration and dissemination, to raise standards of care for infants born with CL/P, and to improve knowledge on the genetic and environmental risk factors with a view to primary prevention.

2.11 Cleft research organisations and projects

2.11.1 World Health Organisation (WHO)

This is one of the largest global organisations responsible for health within the United Nations system. It has a crucial role in raising the standard of care across all branches of health. Among the many roles, it formally co-ordinates authorities and provides leadership on worldwide health issues and threats with the help of WHO collaborating centers. It functions to provide support to countries that require assistance in implementing standards and is the main contributor for developing knowledge, research and birth surveillance in orofacial clefting.

2.11.2 Global Burden of Disease project (GBD)

The GBD project, established by the WHO, has a principle aim to gather information on mortality and morbidity rates. Since its first study in 1990, the project has grown in its ability to deliver, disseminate and provide guidance on health information, so that countries can formulate and implement effective health strategies. Craniofacial research has a part to play in this large project. Increasing our knowledge in this field through the international collaborative research on craniofacial anomalies project will help identify risk factors for mortality and morbidity rates.

2.11.3 International collaborative research on craniofacial anomalies project.

This project is strongly supported by the WHO and the GBD project. It was established to determine the genetics, prevention, risk factors and ideal treatment practices for craniofacial research on a global scale. International collaboration has led to significant advancements in this field with many anomalies now mapped to particular genetic loci. Birth surveillance for orofacial clefting is an important determinant for epidemiology and an assessment of both hereditary and environmental risk factors (Sections: *2.10.4 Eurocleft project/ 2.10.5 Eurocran/ 2.10.6 Euroclftnet*).

2.11.4 Birth Surveillance in orofacial clefting

Many global registries have been established over the last few decades. However, there are many challenges that lie ahead to complete a full birth surveillance record for all patients born with orofacial clefting. The key organisations responsible for reporting birth surveillance and research are as follows:

1) International Clearinghouse for Birth Defects Surveillance and Research (ICBDSR)
2) European Surveillance of Congenital Anomalies (EUROCAT)
3) National Birth Defects Prevention Network (NBDPN)
4) The Latin American Birth Defects Surveillance Registry (ECLAMC)

The GBD project aims to map the birth prevalence of OFC across the world, and therefore a major mission for the WHO collaborating centers in Dundee is to encourage countries who do not have birth defect registries to set these up.

2.11.5 Cleft Care Scotland (CCS)

The Cleft Care Scotland network is comprised of a number of representatives from different specialties involved in cleft care across Scotland. It aims to deliver the Scottish Government Health Directorates Healthcare Quality Strategy of consistent high quality care. Managed Clinical Networks have been established with peer review forums of practices and outcomes in order to develop clear guidelines that units across Scotland can follow. Cleft Care Scotland is also involved with integration of its findings and implementations with the second CSAG investigation, known as Cleft Care UK.

2.12 Assessment of outcomes in CL/P

Robust outcome measures have contributed greatly to facilitating multicentre comparisons, streamlining study design, research dissemination and establishing superiority of one intervention over another. Outcome indices should be simple, acceptable, objective, reliable are should be amenable to statistical analysis (World Health Organisation, 1977). For universal use they should not be restrictive in terms of language.

2.12.1 Early scoring systems for patients with unilateral cleft, lip and palate.

Early scoring systems were largely descriptive investigating pre-surgical orthopedics and bone grafting by determining the presence of crossbites in the complete maxillary dentition (Pruzansky and Aduss, 1964). Surgical outcomes for patients with unilateral and bilateral cleft lip and palate were described by a three tier alphabetical categorical classification system (Matthews et al., 1970). Categories representing perfect class I occlusion (category A), through to class III occlusion with some part of the dental arch collapsed (category C).

2.12.2 The Huddart Bodenham Scoring system

This numerical scoring system evaluates operative procedures using arch form and occlusion for patients in the complete deciduous dentition with UCLP (Huddart and Bodenham, 1972). The maxillary arch is divided into three segments, and each tooth (excluding lateral incisors as they are commonly absent in patients with CL/P) is individually assigned a score owing to its relation with the corresponding opposing tooth (Figure 8).

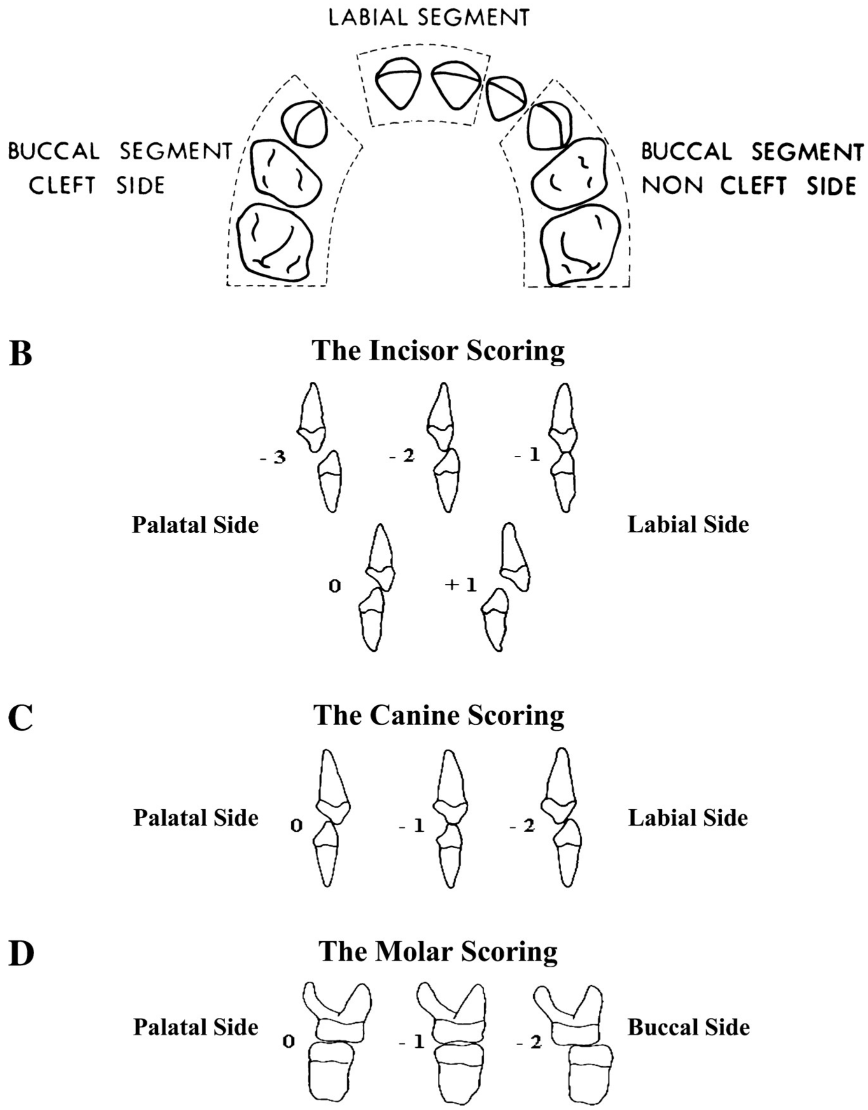


Figure 8: Huddart Bodenham segmental divisions and dental arch relationship scoring categories.

The reliability of this system was found to be poor when compared with Pruzansky's descriptive classification owing to a greater number of categories (Huddart and Bodenham, 1972). Greater reliability was found when a ±1 or ±2 categorical difference in the total malocclusion score was accounted for.

This system offers greater evaluation of the severity of a malocclusion, and is amenable to statistical analysis. It is limited for use in younger patients and not those patients aged 12-13 years when orthodontic intervention maybe best suited, or where a complete maxillary deciduous dentition is absent. This is a problem given that children with cleft lip and palate often suffer with high caries rates, hypodontia and supernumerary teeth (Shapira et al., 2000, Dahllof et al., 1989).

2.12.3 The GOSLON Yardstick

The GOSLON Yardstick, named after the Great Ormond Street, London, Oslo and Norway centers, assesses dental arch relationships in patients with UCLP (Mars et al., 1987). Designed for use in the late mixed or early permanent dentition, it provides an indication of treatment complexity and expected treatment outcome. It categorises the severity of a malocclusion into 5 grades.

- Group 1 — Excellent — Straightforward treatment or no need for treatment. Favourable outcome expected.
- Group 2 — Good — As above with slightly more complex treatment needed.
- Group 3 — Fair — Complex orthodontic treatment required to correct a class III malocclusion but a good outcome is anticipated.

- Group 4 — Poor — Borderline orthodontic-only treatment. Orthognathic surgery will be required if facial growth is unfavourable.
- Group 5 — Very poor — Orthognathic surgery will be required for occlusal outcomes to be satisfactory.

Dental arches are subjectively rated by the anteroposterior, transverse and vertical labial segment relationships of the dental arches. The anteroposterior relationship is regarded as the most clinically significant of the three features of malocclusion, with features such as irregularity of teeth being relatively unimportant. Both intra-observer and inter-observer reliability has been shown to be high (Mars et al., 1987) and has been valuable in determining the multicenter comparisons of surgical outcomes of patients with UCLP (Shaw et al., 1992).

Limitations of the GOSLON Yardstick include the lack of precise delineation between the classification groups, leaving borderline cases challenging to rate and requiring subjective professional judgment (Mossey et al., 2003). Assessors intending to use this system require calibration and reference models, which is costly and time consuming. The system is not designed for the deciduous dentition and consequently, surgeons are not able to obtain meaningful personal outcome data for primary palate repair until the mixed dentition is present with this index (Jones et al., 2014). A different index would be required prior to this time point. The five broad categories make it open to significant error if a one or two category difference is scored (Gray and Mossey, 2005). Lastly, the categorical data makes statistical analysis limited.

2.12.4 5 Year old index

This is a modified GOSLON Yardstick classification system for use on study models of children aged 5 years in order to determine early surgical outcomes (Atack et al., 1997). It uses the same 5 GOSLON Yardstick categories to rate the dental arches. It has been demonstrated to be a reliable comparison with the dental arch relationships in patients born with UCLP (DiBiase et al., 2002). This system, like the GOSLON Yardstick also requires calibration for competent use, reference models and is restricted for use in patients with UCLP (Jones et al., 2014).

2.12.5 The Modified Huddart and Bodenham (MHB) scoring system

Recognition of the limitations of existing scoring systems led to preliminary investigations to develop a numerical scoring system measuring maxillary arch constriction in patients with UCLP, for use at any age (Mossey et al., 2003). Modification to the original Huddart and Bodenham scoring system adapted the scores for deciduous teeth to permanent teeth.

Using this system, all teeth forward of the first permanent molar are allocated a score with the exception of the lateral incisors (Figure 9). Teeth are graded either positively or negatively depending on their buccal or palatal relationship with the corresponding lower tooth. Premolars are assigned a score in a similar fashion as for the deciduous molars. Unerupted or missing teeth are allocated a score using the midpoint of the maxillary alveolar ridge as a reference point for assessment with the opposing tooth. Where one premolar is unerupted, but the other is present, the reference for the unerupted tooth is viewed at the same bucco-lingual position as the erupted premolar. In the case that two premolars are unerupted the midpoint of the ridge is taken as the reference.

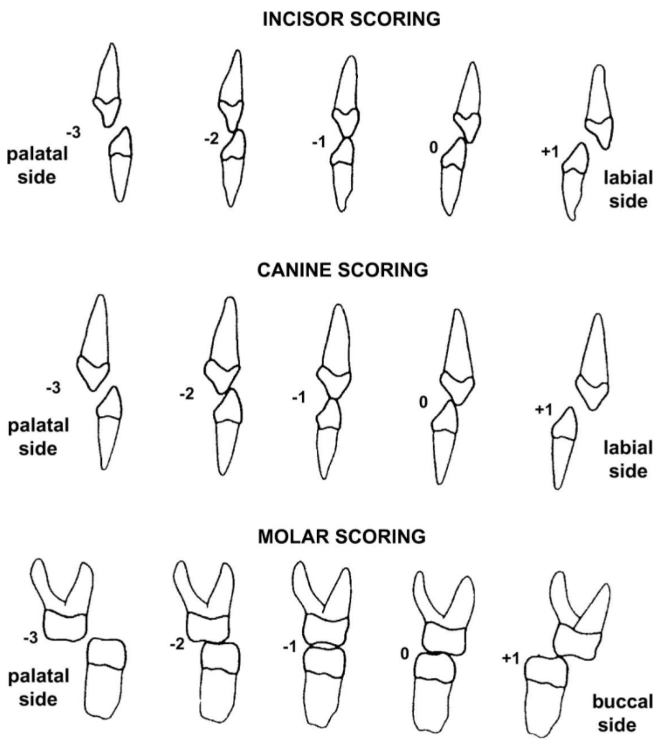


Figure 9: Modified Huddart Bodenham dental arch relationship scoring categories (Dobbyn et al., 2012).

Summation of scores from the 10 pairs of teeth (i.e. two incisors, two canines, four premolars, two molars), provides a total overall score between -30 and +10. If the patient is older than 6 years of age, these 10 pairs of teeth are scored as outlined above. For patients younger than 6 years, the first permanent molars are not scored, therefore only 9 pairs of teeth are scored giving a range of scores between -24 to +8.

The MHB system has been recommended as the index of choice in cleft care (Altalibi et al., 2013). It has versatility, facilitating surgical outcome assessment in patients of any age from 3 years and up (Mossey et al., 2003, Gray and Mossey, 2005, Dobbyn et al., 2012), and is reliable for patients with other cleft subtypes such as bilateral cleft lip and palate and isolated cleft palate (Tothill and Mossey, 2007). This single system allows a series of models to be scored as each patient progresses through their cleft care pathway, facilitating direct comparison of surgical interventions within and between individual patients. Multicentre research comparisons are simplified through a more consistent method and as calibration is not required, any clinical or non-clinical staff member can use the scoring system (Tothill and Mossey, 2007). The continuous scale used to confer the severity of malocclusion is more sensitive than previous discrete descriptive categories of other classification systems, where the severity of the malocclusion within the category is unknown (Mossey et al., 2003). Lastly, the numerical aspect of the system lends itself to further calculations and application to computer based programming where previous subjective approaches would be difficult (Gray and Mossey, 2005).

2.12.6 EUROCRAN Yardstick

The Eurocran Yardstick is a two tier modification of the GOSLON Yardstick and 5 year indices (Oskouei, 2007). It primarily focuses on three aspects of a malocclusion: anteroposterior relationships of teeth, palatal morphology and vertical dimension. It has four grades to rate the anteroposterior dental arch relationship unlike GOSLON Yardstick, which has 5 categories and 3 grades to rate the palatal morphology. In a retrospective study this index performed inferiorly when compared to the MHB scoring system in terms of user-friendliness, however it was a faster index for scoring models of patients with UCLP (Patel, 2011). Reliability of the index for palatal morphology is moderate (Fudalej et al., 2011), but further validity and reliability testing of the index is required (Jones et al., 2014).

2.12.7 BCLP Yardstick

The BCLP Yardstick is a clinical tool for assessing surgical outcome in patients with Bilateral Cleft lip and Palate (Ozawa et al., 2005, Bartzela et al., 2010). It is a further modification of the GOSLON Yardstick and in a similar fashion grades a malocclusion using a five point categorical scale. There are three different Yardsticks for various stages of development: '6 year olds' Yardstick', '9 year olds' Yardstick' and the '12 year olds' yardstick'. It requires reference models for use and has been shown to be comparable to the Huddart and Bodenham system (Bartzela et al., 2011).

2.12.8 Outcome indices and photographs

There have been a number of studies that have investigated the use of intra-oral photographs for use in assessing dental arch relationships for UCLP patients (Nollet et al., 2004, Liao et al., 2009, McAuliffe et al., 2011, Jones et al., 2015). Results from these studies show they can be used as an alternative for assessing surgical outcomes, however Jones et al suggest they may not be as reliable at the gold standard plaster models (Jones et al., 2015). Where photographs are to be used high-quality standardised photographs are mandatory. Standardisation of photographs between centres can be difficult and good quality intra-oral views in young patients can be particularly challenging. Furthermore, the use of 2D photographs also leads to problems with the perception of depth, which can be deceiving in patients with a large overjet.

2.12.8 Outcome indices and digital models

Since the 1970s technology for digital study models has been available for restorative and orthodontic use. During the 1990s it became widely popularised and accepted (Harradine et al., 1990, McGuinness and Stephens, 1992, Mah, 2007). A high degree of correlation exists between measurements made on plaster study models and those on digital images (Fleming et al., 2011).

Research has validated the use of digital models for the assessment of routine orthodontic outcomes indices such as the Index of Orthodontic Treatment Need (IOTN) (Sharma et al., 2013).

The GOSLON Yardstick has shown good intra-observer and inter-observer reliability between plaster and digital study models (Nicholls et al., 2014). Validation of the MHB scoring systems and GOSLON 5 year old index on digital study models has been demonstrated in patients with UCLP (Asquith and McIntyre, 2012, Chawla et al., 2013). Reference models for the GOSLON Yardstick can also be scanned to complete the virtual scoring process of surgical outcomes for orofacial clefting. Inherent to all the comparative studies using digital models is the use of manual methods of assessment for scoring with the indices.

2.13 Archform

Comparing the differences between maxillary and mandibular archforms can assess dental arch relationships. Archform is an integral part of any dental treatment as it dictates the parameter for the spatial relationship of teeth. The literature describes several 'ideal' archforms namely conic sections, polynomials, beta functions, geometric curves, and catenary curves. However adaptation of the archform will be required if stability of the occlusion is to be maximised (Little, 1990, Felton et al., 1987).

2.13.1 Bonwill and Brader archform

Bonwill's early geometric concept of archform was based on an equilateral triangle (Angle, 1899). It was subsequently modified with the addition of an arc where the radius is dependent on the mesio-distal widths of anterior teeth (Hawley, 1905). Other basic shapes defined to be ideal are square, tapered and ovoid archforms (Chuck, 1934) which are still used in the conventional MBT (McLaughlin-Bennett-Trevisi) orthodontic appliance systems (3M Unitek, Monrovia, California).

Early computerised methods to determine optimal dental archform have suggested that the ellipse provides a superior guide over the parabola (Currier, 1969). Brader defined a mathematical model, PR=C, for a trifocal elipse as applied to the maxillary and mandibular arches in relation to the soft tissue forces (Brader, 1972). P represents pressure from soft tissue forces in Gm/cm^2, R, the radius of curvature of the elliptic curve at the site of pressure in mm, and C a mathematical constant. Both the work by Brader and Currier have been critised for referring to archforms of 'average shapes' without defining the meaning of this (Sampson, 1981).

2.13.2 Catenary curves

The mathematical concept of the catenary curve of form $y=(e^x + e^{-x})/2$, for the occlusal contact points (MacConaill and Scher, 1949), describes a simple shape formed by a length of chain that hangs down with gravity between two hooks. However, it was recognised that it was not possible to use one archform, such as the catenery curve for all patients due to individual variation (Felton et al., 1987). On examining samples of extraction, non-extraction and untreated archforms, none of the 17 commercially available arch forms were appropriate for the majority of cases.

2.13.3 Polynomial function and conic sections

Algebraic modeling of archform includes the use of polynomial equations of varying degrees from 2nd to 6th order (Pepe, 1975), or statistical modeling of archform using conic sections, the simplest family curves derived from the intersection of planes with cones (Sampson, 1981). There are four types of simple conic arcs; ellipse, parabola, hyperbola and the circle. Sampson recognised the need to carefully justify the landmarks for analysis when defining an archform as this will determine the suitability for use. The underlying symmetry in these functions are limiting when describing inherently asymmetric archforms.

2.13.4 Euclidean Distance Matrix analysis

The Euclidean distance is the distance between two points in metric space. Ferrario uses the Euclidean Distance Matrix analysis (EDMA) model to examine dental symmetry, while Nie and Lin used this method to compare malocclusions with 'normal' occlusions as an aid to treatment planning (Nie and Lin, 2006, Ferrario et al., 1993). Both author groups found that the EDMA method was superior in describing size and shape and major variations between hemi-arches.

2.13.5 Cubic splines

A cubic spline is essentially a connection of a series of 'knots' or points into a smooth curve, irrespective of arch size. BeGole's work describes the use of a cubic spline from digitised data sets using x and y co-ordinates (Begole, 1980). It was further developed into a 2D planar computerised program for dental archform analysis (Begole, 1979).

Found to be a suitable method of archform analysis in well-aligned arches, it was not affected by asymmetry. It could be used for describing 'normal' and 'abnormal' occlusions in addition to changes in the dental arch as a result of treatment. Developments into 3D geometric shape, the Cartesian x, y, and z co-ordinates were described for the use with occlusal curves and EDMA, using a 3D digitiser from plaster study models (Ferrario et al., 1993).

2.13.6 Digital archform

The advent of digital models opened a new avenue for dental archform research. Initially 2D planar geometric shapes such as the application of a fourth degree polynomial curve and the β function (Adaškevičius and Vasiliauskas, 2009), using 12 identified digital landmarks to define the curve (Figure 10).

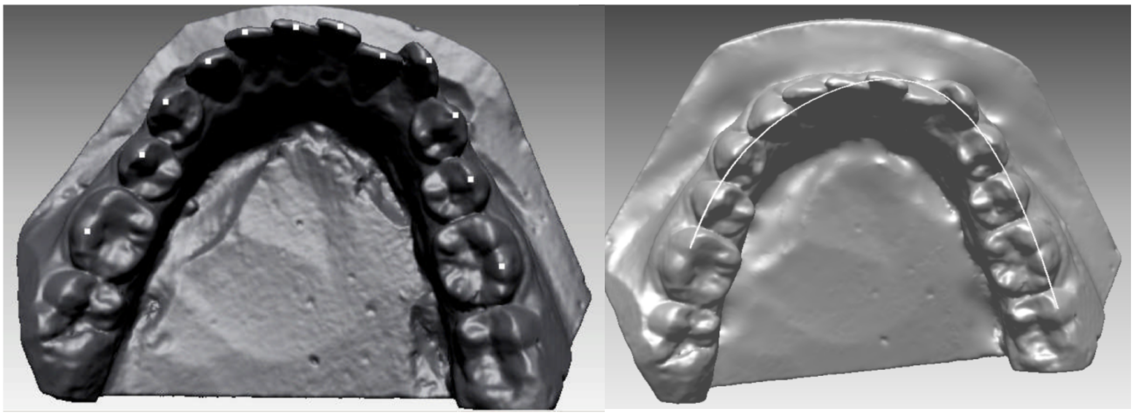


Figure 10: Digital mandibular models displaying digitally identified landmarks and a polynomial curve (Adaškevičius and Vasiliauskas, 2009).

These archforms did not take into account the true spatial relationship of each digitally identified landmark as it ignored the vertical component of archform.

Overcoming the shortfall of 2D planar geometry, a statistical model for shape analysis was derived from the Generalised Partial Procrustes Analysis (GPPA) (Bookstein, 1991, Dryden and Mardia, 1998, Nam et al., 2012). It is particularly useful in the generalised form when comparing the 'optimal mean shape' to three or more superimposed shapes. One study used 52 selected digitised landmarks to calculate the centroid used for scaling of their arbitrary reference configuration (Nam et al., 2012). Superimposition of the remaining configurations of arch form on this arbitrary reference configuration can be assessed when located about a set point.

2.13.7 Archform in CL/P

In normally formed dental arches the archform resides within the equilibrium of pressure formed by the surrounding soft tissues. When an arch is malformed within CL/P the balance of forces is upset and there is a lack of consistent pressure from the obicularis oris, buccinators and superior constrictor muscles, resulting in displaced segments of the dental arch (Berkowitz, 2013). The degree of displacement of the dental alveolus will depend largely on the location, severity of the cleft and soft tissue morphology. Where a complete cleft of the lip and palate has separated from the vomer, it loses hard tissue support. In addition, the tongue becomes more superiorly positioned, filling the region of the cleft pushing segments laterally or anteriorly, contributing to a disruption of the original archform.

Understanding dental arch morphology in orofacial clefts, both in patients who have been treated surgically and those who have not, has been essential in establishing the degree of maxillary arch constriction and comparing outcomes of various treatment protocols (Shaw et al., 1992, da Silva Filho et al., 1992). Archform can be assessed pre and post eruption of teeth. It is the mainstay for the assessment of maxillary constriction when investigating the effects of pre-surgical orthopaedic appliances, different surgical techniques and timing of cleft repair (Adali et al., 2012, Sasaguri et al., 2014). Assessment of archform in the vertical, anteroposterior and transverse planes are essential for accuracy.

2.14 Further research for dental arch relationships

Research has focused on establishing the use of digital study models as an acceptable medium for assessing surgical outcomes in cleft care. The validity, reproducibility and reliability of digital models when compared to conventional plaster models of teeth has been proven (Fleming et al., 2011, Chalmers, 2015). The single biggest procedural difference between scoring digital models and plaster models are that digital models must be viewed, rotated and manipulated virtually rather than holding and manipulating plaster models physically. Therefore, the limitations of manual scoring, such as the inherent subjectivity of categorising malocclusions, are carried over to digital scoring, i.e. the same method of scoring is used for both mediums.

The next step in developing accurate scoring systems in cleft care is to develop a software tool to facilitate efficient, more robust, and objective methods of assessment. The tool would enable users to effectively score digital study models through simple tasks outlined by the software. The focus of this research project is the development, calibration and validation of such a software tool. This is a new innovation for cleft care that could be utilised in the developed and developing world.

CHAPTER THREE: AIMS, OBJECTIVES & HYPOTHESES

3.1 Aims

This project aims to design, develop and test a software tool for the 3D analysis of archform to enable the automatic calculation of the Modified Huddart and Bodenham scores for patients with cleft lip and/or palate.

3.2 Objectives

1) To design and develop a software tool for automatic MHB scoring on digital study models.
2) To calibrate the automated scoring tool for calculating MHB scores on digital models of patients with UCLP.
3) To validate the automated scoring tool for calculating MHB scores against conventional methods of MHB scoring.
4) To determine the intra-observer and inter-observer reliability and reproducibility for using this digital scoring system compared to manually scoring digital study models.

3.3 Null Hypotheses

1) MHB scores determined using the Rhinoceros, version 5 (Rhino)(www.rhino3d.co.uk) (Robert McNeel & Associates, 2014) plug-in are no different to those determined using existing methods with digital and plaster models.

2) Measurements using the Rhino plug-in software are no different to those made on conventional plaster models.

3) The time taken to produce MHB scores using the Rhino plug-in is no different to using existing methods with digital and plaster models.

CHAPTER FOUR: MATERIALS AND METHODS

4.1 Methodology

This project was split into a series of discrete stages.

1) Design and development of the algorithm to accurately generate horizontal and vertical measurements for teeth on digital models.
2) Coding the algorithm into a software platform for clinical use as a software tool.
3) Conversion of the horizontal measurements generated by the software tool into MHB scores.
4) Calibration of the software tool.
5) Validation of the software tool.
6) Investigation of the relative error of landmark identification on digital models.
7) Time efficiency investigation of the algorithm.

4.2 (1) Design and development of the algorithm

Digital models, in an STL file format, from a population of subjects with UCLP were obtained for development of the algorithm (Section: *4.10.3 Study population*).

4.2.1 Non-Uniform Rational B-splines (NURBS) and T-spline reconstruction

The large amount of linear surface data supplied by an STL file of a digital model is complex to handle. Therefore it was simplified and reconstructed to form a smooth 3D surface model that looks familiar to clinicians as a digital model. This was achieved with Non Uniform Rational B-splines (NURBS), subdivision surfaces and T-splines.

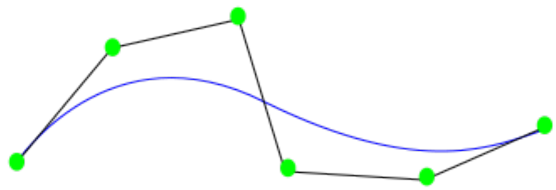


Figure 11: NURBS curve passing through a series of control points (Wang and Zheng, 2013).

NURBS are mathematical models that represent curves and surfaces (Rogers, 2000), and are commonly used within computer aided design (CAD) (Figure 11). Subdivision surfaces improve the smooth contour of the 3D images by significantly increasing the number of vertices and faces in a given mesh. It recursively subdivides the faces on the mesh through mathematical algorithms, whilst retaining the original form of the shape (Ma and Cripps, 2011). T-splines are a very useful CAD technology that can unify multiple NURBS surfaces needed for complex morphology. T-splines have been formally described for degree 3, where one control point connects to 2 other control points (Sederberg et al., 2003). Application of T-splines reduces the number of superfluous control points in the linear data mesh. The aforementioned mathematical modeling was achieved using automatic rendering functions in a software platform that accommodated STL data formats.

4.2.2 Landmark identification

Digital landmarks, identified by the clinician, were required to instruct the software of the maxillary and mandibular parameters, for calculation of horizontal and vertical measurements. Conventional methods of MHB scoring use a subjective assessment of the anatomical landmarks for maxillary and mandibular teeth. Therefore, formal definitions of the digital landmarks were determined as follows (Figure 12):

- Most buccal point on the groove between the mesial and mid buccal cusps of the lower first or second molar, or any deciduous molar.
- Buccal cusp tips of the first and second premolars, where erupted.
- Cusp tip of the canines.
- Mid-point of the incisal edges for all incisors.

The molar groove was used to minimise any discrepancy due to molar rotation.

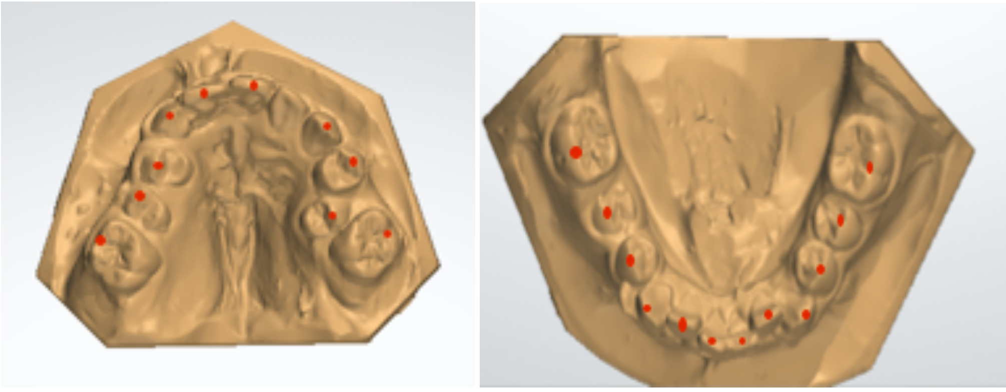
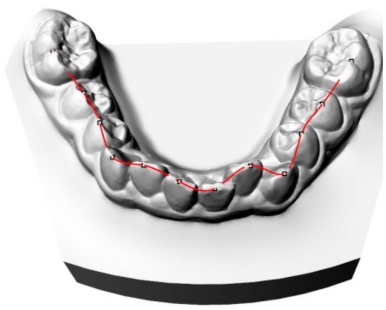


Figure 12. Digital landmarks used for development of the MHB automated scoring software.

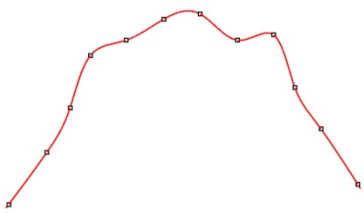
4.2.3 Development of a 3D cubic spline archform

To compare the relative archforms of the maxillary and mandibular arches, the mandibular arch was used as a reference, to which the maxillary arch was compared. A mandibular archform, accurately representing the dental archform in all 3 planes of space, was created using a cubic spline (Figure 13). A spline using third order polynomials was used as this facilitated good flexibility and accuracy, whilst limiting the number of calculations needed to produce the cubic spline. An algebraic formula on a cartesian co-ordinate system using the mandibular digital landmarks, is represented as Pixi,yi,zi, i=1,⋯,n, which results in a mathematical expression for a cubic spline (Appendix II).



(a) Perspective view

(b) Buccal view



(c) Occlusal view

(d) Anterior view

Figure 13. Cubic splines visualised from different perspectives.

4.2.4 Fitting of a reference plane

Mathematical vectors were used to generate distances between the identified maxillary control points (anatomical landmarks identified) and the lower mandibular cubic spline. These vectors required a reference plane to orientate the horizontal dimension. An occlusal plane demarcated by the cusp tips of the mandibular model was used, assuming that using the mandibular model for this plane was unaffected in the vertical and horizontal dimensions by the clefting defect. A plane that best fitted the mandibular control points, Pixi,yi,zi, i=1,⋯,n, using a least square fitting technique, minimising the sum of the squares from the residuals (mandibular control points) to the spline was identified (Figure 14). Measurements for the dimensions of 10 teeth scored in the current MHB scoring system using horizontal and vertical vectors between the maxillary and mandibular arches were undertaken. ***n*** is the normal of the reference plane. It is usually pointing to upwards.

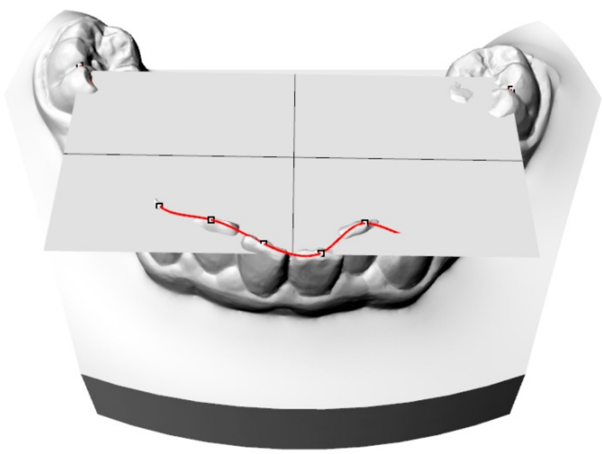


Figure 14. Mandibular reference plane

4.2.5 Comparison of maxillary and mandibular arches

Horizontal and vertical dimensions were calculated using the nearest distance of the maxillary control points identified to the mandibular cubic spline. Maxillary cusps were represented as Qjxj,yj,zj, j=1,⋯,m, and the nearest points on the cubic spline represented as Qj'xj',yj',zj', j=1,⋯,m. Therefore the nearest distance of maxillary cusps Qj to the cubic spline S was dj=Qj-Qj'. Subsequently the horizontal distance dhj was the projection of dj to the horizontal reference plane. The vertical distance dvj was the projection of dj to the normal of the horizontal reference plane.

Adaptation of the algorithm was made to ensure that the sign for the horizontal dimension correlated with what would be expected of a bucco-lingual relationship. It was expected that the horizontal distance was positive when the maxillary cusps were sited buccally to the buccal cusps of the mandibular teeth and negative sign for a clinical buccal crossbite where the buccal cusps of the maxillary teeth occlude lingually to the buccal cusps of the mandibular teeth. Using tangents to the cubic spline with a direction that is consistent with the order of sampling of mandibular cusps (i.e. landmark identification from right to left when viewing the curve), this could be achieved (Figure 15) (Appendix II).

A.

B.

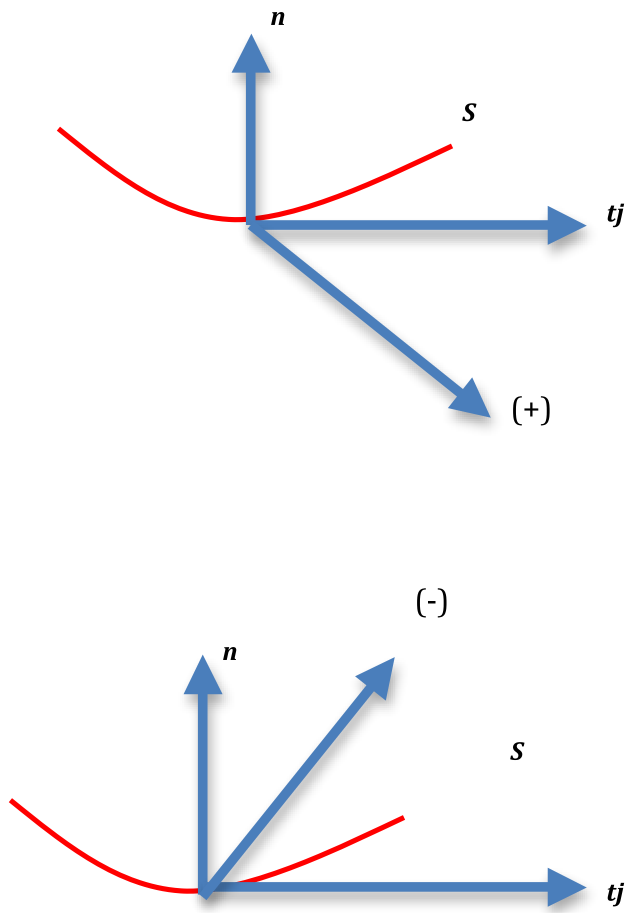
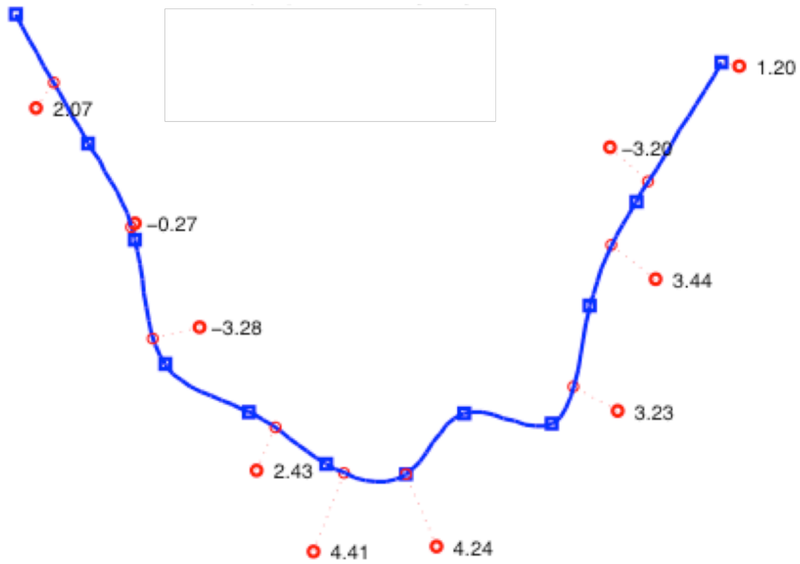


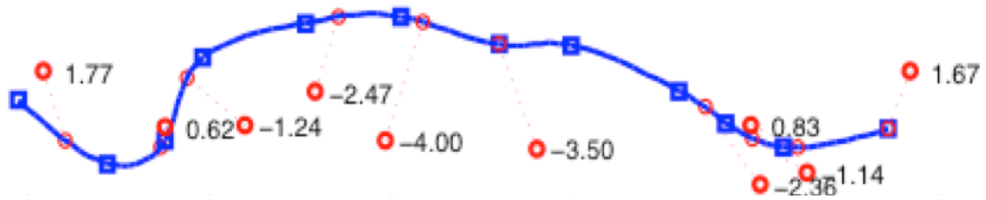
Figure 15. Image showing tangential vectors to determine the sign of the horizontal and vertical dimensions. A. Buccal cups of the maxillary teeth are buccal to the buccal cusps of the lower teeth (+) B. Buccal cusps of the maxillary teeth are lingual to the buccal cusps of the lower teeth (-). *n* denotes the normal of the reference plane. *tj* denotes the tangential vector to the cuspic spline *S*.

4.3 (2) Coding the algorithm

Development and coding of the algorithm initially took place in MATLAB®, a numerical computing environment software, as it was readily available for the implementation of algorithms and plotting functions. Over the period of January 2015 to May 2015 the algorithm was tested, modified and re-tested at regular joint meetings with collaborators on the project. Once the algorithm was performing as expected, horizontal and vertical dimensions were generated for each tooth pair (included in MHB scoring) for the study population of digital models. Images were produced for every digital model to enable visualisation of the cubic splines and identify any technical problems (Figure 16).



A.



B.

Figure 16. Image generated in MATLAB for the calculation of horizontal and vertical dimensions in mm between maxillary cusps and the mandibular cubic spline curve. Red dots denote maxillary cusps identified, blue dots denote mandibular cusps identified. A. Horizontal cubic spline B. Vertical cubic spline.

One complexity became apparent after early testing of the algorithm. For severe class III malocclusions, the lower cubic spline did not extend far enough distally to correspond with the upper maxillary cusps. This exaggerated the distance between the upper maxillary molar landmark to the mandibular spline. To overcome this, adaptation of the algorithm was made to include the lower second molars in the cubic spline. This extended the spline far enough distally to accommodate for class III discrepancies, which are often present in patients with CL/P. Following this, the algorithm was transcribed using Visual Basic Language (VBL), into a larger software platform Rhinoceros, version 5 (Rhino)(www.rhino3d.co.uk) (Robert McNeel & Associates, 2014), as a reliable plug-in script (Section: *4.10.2 Software platform and computing requirements*).

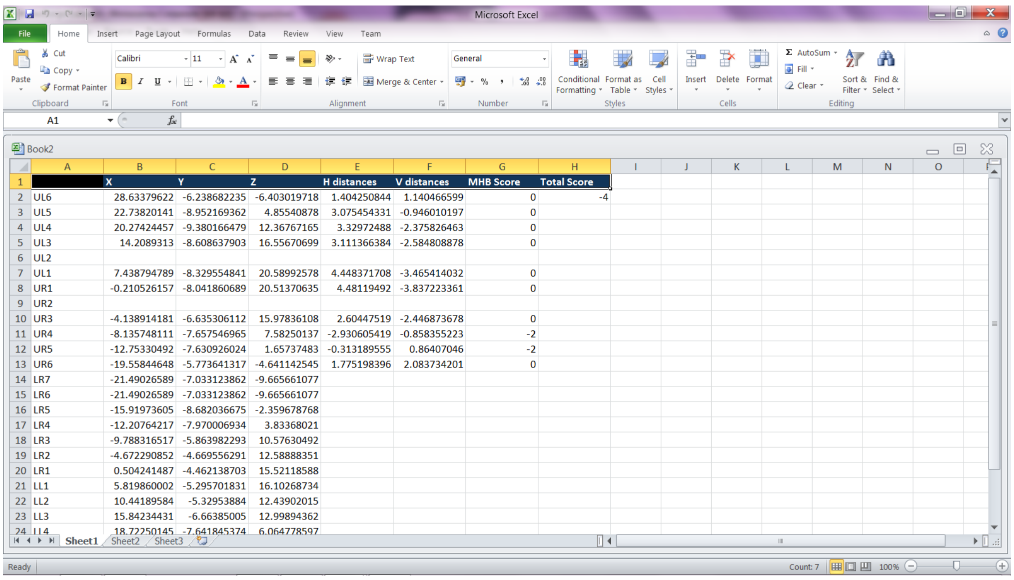
4.4 (3) Comparison and conversion of horizontal measurements to MHB scores

The Rhino plug-in was able to generate 10 horizontal and vertical vector distances. Conversion of these distances to MHB scores was achieved by correlating the results of manual MHB scores from one Orthodontic Consultant, experienced in cleft care, with cumulative horizontal distances for the right, left side and incisor region of the dental arch produced by the algorithm. A group discussion of the distance parameters for MHB scores took place between the investigator (CM) and research supervisors to ensure agreement. The MHB scores for a range of horizontal measurements were then coded into the Rhino plug-in (Table 2).

Table 2. Corresponding MHB scores to horizontal distances in mm.

MHB Score to be assigned	Horizontal distance (h) in mm
+1	h ≥ 4.5
0	4.5 > h ≥1.2
-1	1.2 > h ≥ -0.3
-2	-0.3 > h ≥ -3.3
-3	-3.3 > h

The Rhino plug-in was instructed to output the results for landmark co-ordinates, horizontal and vertical distances, MHB scores for each tooth, and total MHB scores, into an Excel spreadsheet (Microsoft 2013) (Figure 17). Sequential operation of the Rhino plug-in script can be viewed in Appendix III.



	X	Y	Z	H distances	V distances	MHB Score	Total Score
UL6	28.63379622	-6.238682235	-6.403019718	1.404250844	1.140466599	0	-4
UL5	22.73820141	-8.952169362	4.85540878	3.075454331	-0.946010197	0	
UL4	20.27424457	-9.380166479	12.36767165	3.32972488	-2.375826463	0	
UL3	14.2089313	-8.608637903	16.55670699	3.111366384	-2.584808878	0	
UL2							
UL1	7.438794789	-8.329554841	20.58992578	4.448371708	-3.465414032	0	
UR1	-0.210526157	-8.041860689	20.51370635	4.48119492	-3.837223361	0	
UR2							
UR3	-4.138914181	-6.635306112	15.97836108	2.60447519	-2.446873678	0	
UR4	-8.135748111	-7.657546965	7.58250137	-2.930605419	-0.858355223	-2	
UR5	-12.75330492	-7.630926024	1.65737483	-0.313189555	0.86407046	-2	
UR6	-19.55844648	-5.773641317	-4.641142545	1.775198396	2.083734201	0	
LR7	-21.49026589	-7.033123862	-9.665661077				
LR6	-21.49026589	-7.033123862	-9.665661077				
LR5	-15.91973605	-8.682036675	-2.359678768				
LR4	-12.20764217	-7.970006934	3.83368021				
LR3	-9.788316517	-5.863982293	10.57630492				
LR2	-4.672290852	-4.669556291	12.58888351				
LR1	0.504241487	-4.462138703	15.52118588				
LL1	5.819860002	-5.295701831	16.10268734				
LL2	10.44189584	-5.32953884	12.43902015				
LL3	15.84234431	-6.66385005	12.99894362				
LL4	18.72250145	-7.641845374	6.064778597				

Figure 17. Excel spreadsheet (Microsoft 2013) displaying the output of the Rhino script with horizontal, vertical distances and MHB scores.

<u>4.5 (4) Calibration of the novel software</u>

Prior to validation of the automated system on a study population of subjects with UCLP, examiners were calibrated to ensure standardisation of the scoring process. Written and verbal scoring instructions were provided to three examiners (Appendix IV). These were as follows:

- Consultant Orthodontist and Craniofacial anomalies expert
- Orthodontic Consultant involved in cleft care
- Orthodontic Specialty Training Registrar (Chief investigator)

<u>4.6 (5) Validation of the novel software</u>

The Rhino plug-in was tested against conventional methods of MHB scoring on plaster models and digital models. Fifty-three subjects were available for the study (Section: *4.10.3 Study population*). The scoring process for manual and the Rhino- plug-in is displayed in Figure 18.

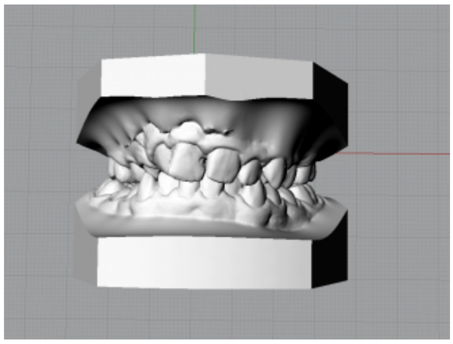
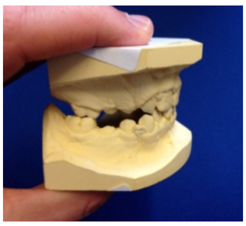
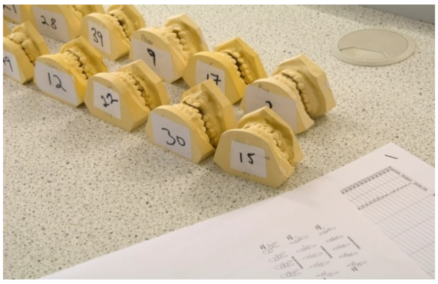
Manual MHB scoring	Automated MHB scoring
Step 1. Plaster model present for scoring. 	**Step 1.** Digital model present for scoring. 
Step 2. Manipulation of the plaster models to assess the bucco-lingual relationship for each corresponding tooth pair.  	**Step 2.** Identify cusp tips on the maxillary teeth used for MHB scoring and all mandibular cusp tips. 

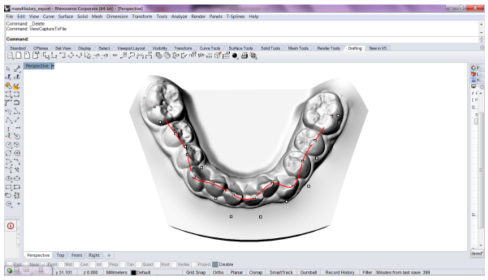
Figure 18. A comparison of the automated and manual methods of MHB scoring.

Manual MHB scoring	Automated MHB scoring

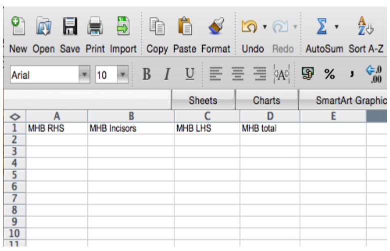
Step 3. Assign subjective bucco-lingual scores according to the MHB scoring criterion. In this example the left buccal segment would score -1,-2,0,0 for each of the tooth pairs, 0,1 for the incisors and 0,-2,-1,0 for the right buccal segments.



Step 3. Automated generation of a cubic spline for the mandibular dental arch with maxillary cusp tips to be used for MHB scoring around it.



Step 4. Manually summate and record the MHB scores in an Excel spreadsheet for each aspect of the malocclusion. The MHB score would be -5 for this individual.



Step 4. Automated output of MHB scores into an Excel spreadsheet. The total MHB score is -5.

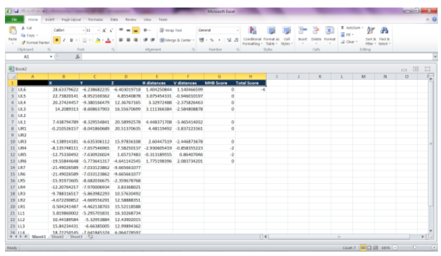


Figure 18 Continued. A comparison of the automated and manual methods of MHB scoring.

The three examiners assessed MHB scores in the study population using three methods:

- Conventional MHB scoring on plaster models.
- Conventional MHB scoring on digital models viewed in OrthoAnalyzer™ software (produced from scanned plaster models).
- Rhino plug-in MHB scores.

Scoring was repeated under similar conditions, 4 weeks apart to test the reliability of the data and facilitate the calculation of inter and intra-observer reliability. Data were recorded in an Excel spreadsheet (Microsoft, 2013).

<u>4.7 (6) Relative error of the method</u>

Potential sources of random and systematic error introduced by digital landmark identification were tested. This error was evaluated by identifying the x, y and z co-ordinates for each digital landmark twice, in the software platform for 28 models. It had been suggested that greater than 25 repeat measurements should be sufficient for detecting systematic error within data (Houston, 1983). This was carried under similar conditions, with a 4-week interval as an appropriate wash-out period.

4.8 (7) Time efficiency investigation of the software tool

Evaluation of the time efficiency of the Rhino plug-in, for calculation of MHB scores over conventional methods of scoring was achieved by recording the total length of time to assess MHB scores in the study population. A digital stopwatch was used to record the time taken by the investigator (CM) to score models for the three mediums. The stopwatch was stopped between each model assessment to eliminate bias due to differences in software and computer capabilities when attaining the digital models on screen.

4.9 Data confidentiality

Data integrity and confidentiality was assured by electronic data file storage on a secure NHS Tayside server. There was no subject identifiable information on any of the digital or plaster models used within this study. Plaster model storage was within the NHS Tayside Orthodontic Department, and made available to each investigator when required. Access to the Rhino software platform was through a University of Dundee secure login desktop computer.

4.10 Materials

4.10.1 Expertise

This project required expertise in clinical dentistry, computer graphics, engineering design, and mathematics. Colleagues from neighboring departments at the Universities of Dundee and Abertay were invited and agreed to work on the project. Regular collaboration through joint meetings was essential for sharing ideas and progress.

4.10.2 Software platform and computing requirements

Two CAD software platforms were required for development and testing of the algorithm. MATLAB® was used initially as it was readily available and could be easily transcribed to a larger software platform, Rhinoceros, version 5 (Rhino)(www.rhino3d.co.uk) (Robert McNeel & Associates, 2014), when needed. Rhino is a commercial research and development software platform, for use with high quality 3D images. Rhino was chosen as it could be operated in Visual Basic and C++.

A computer connected to the University of Dundee Network was available for the project with the specific hardware requirements for Rhino as follows:

- 1 GB RAM. 8 GB or more
- DVD drive or an Internet connection for installation
- 600 MB disk space
- OpenGL 2 capable video card was recommended
- No more than 63 central processing unit cores.
- Windows 7, 8, Vista or XP

Manual scoring of digital models for MHB scores required a laptop with a conventional orthodontic 3D digital viewing software programme. A laptop with a 13.3" backlit LED HD (1366x768) resolution display using 3Shape OrthoAnalyzer™ software (3Shape A/S, Copenhagen, Denmark) was used.

4.10.3 Study population

A sample of patients with UCLP with digital and plaster models were identified from a concurrent study investigating the reliability of digital models for the assessment of surgical outcomes (Chalmers, 2015). A previous sample size of 34 was required at a power of 80% with a p value of <0.05 to highlight a clinically significant difference of > 1 GOSLON category for 2 model formats. To account for potential drop-outs and subjects who would decline to participate, 60 individuals were recruited. The chief investigator (CM) participated in recruitment.

A group of patients with UCLP was therefore identified between the ages of 9 and 21 years from the Cleft Care Scotland database in the Greater Glasgow & Clyde NHS Board area, during the winter and spring of 2013-2014. Patients with suspected or known syndromes, or those patients who were unable to consent due to a lack of capacity or where English was not their native language, were excluded. Prior to the study, patient information sheets were sent to individuals informing them about the study and highlighted that all participation was voluntary. Relevant contact details for further information on the research were issued. These individuals were informed that participation would require a dental impression, a digital intraoral scan and a patient and parent (where relevant) questionnaire.

Fourteen participants failed to attend their appointments and 3 declined participation leaving 43 subjects consenting to the study. Impressions and intraoral scans for the construction of study models were undertaken. Orthodontic impression trays (www.orthocare.co.uk) and alginate (www.unodent.com) impression material were used. The impression material was mixed using an automated mixer (Pulsar MX-300 Alginate Mixer, Motion Medical Supplies & Equipment Corporation, Taiwan) to standardise the mixing technique. A bite registration was taken in dental wax in maximal intercuspation of centric occlusion. One dental nurse carried out decontamination of both wax registrations and impressions. Disinfectant solution (Perform 1D Schulke & Mayr LtD, UK) was used as instructed by the manufacturing guidelines. Impressions were cast into study models using 100% dental stone (Yellow Stone, John Winter & Co Ltd, UK). Although standardisation of the power/liquid ratios of the gypsum was unknown.

A TRIOS intraoral scanner (3Shape®, Copenhagen, Denmark) was used for intraoral scanning, at the same appointment as the dental impressions under standard conditions, however these scans were not used within the study presented in this thesis. OrthoAnalyzer™ digital scans were used in this study and these were obtained by scanning the plaster models in the R700 benchtop scanner (3Shape®, Copenhagen, Denmark)(Figure 19). A single operator carried out the benchtop scanning process.

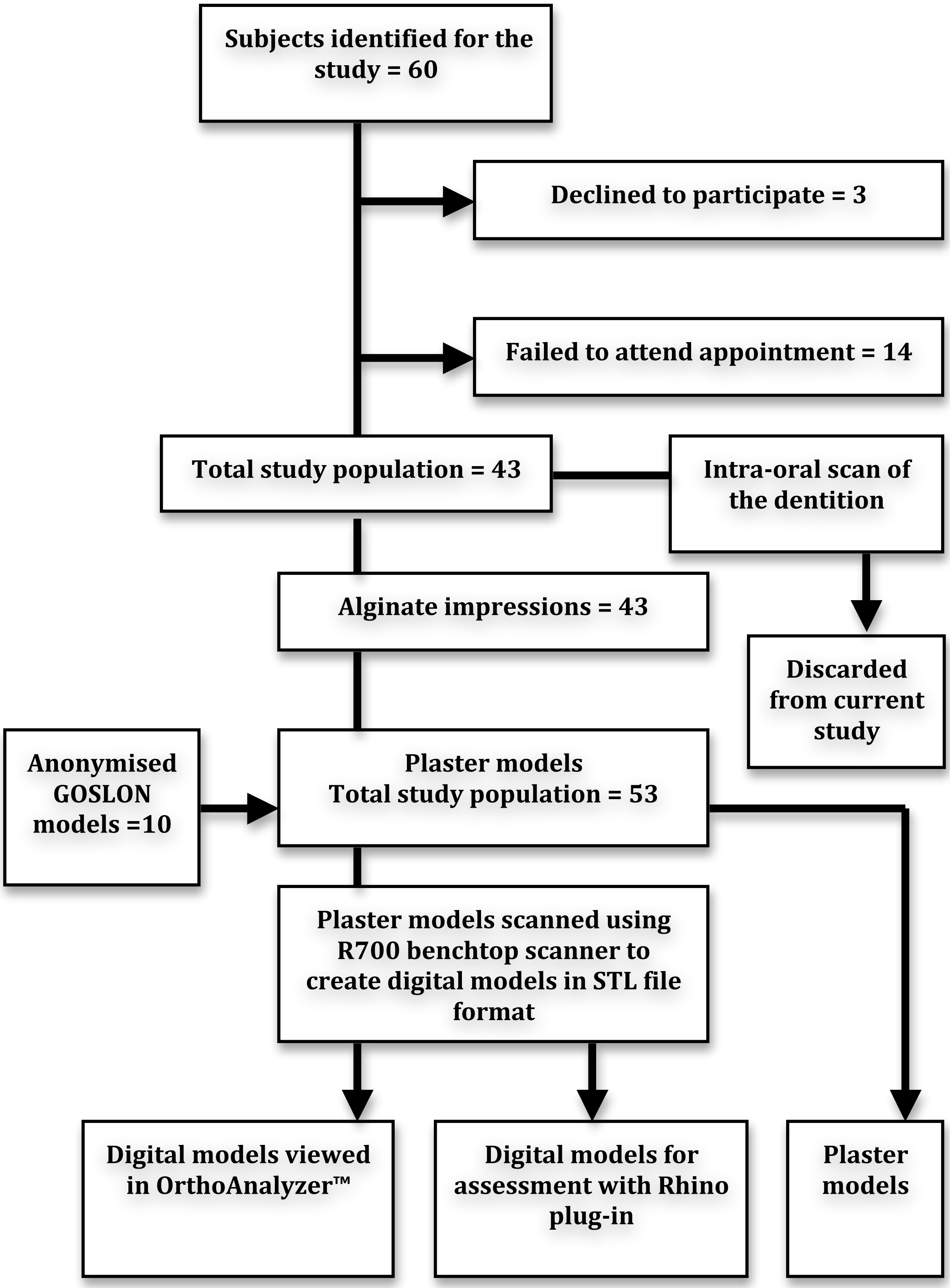
Figure 19: R700 Benchtop orthodontic digital model scanner (3Shape®, Copenhagen, Denmark)

There are currently no specific International standards for which the accuracy of scanners should be used, however most benchtop scanners operate at an accuracy of 20 microns or less (Martin et al., 2015). This includes the R700 scanner.

In addition to the 43 patients with UCLP who had models taken and made available for the study, a further 10 models were added to the sample by anonymising GOSLON anchor models (Figure 20). These GOSLON anchor models were also scanned with the R700 benchtop scanner at the same time as the patient sample. This resulted in the total study sample being 53 plaster and digital models (Figure 21).

Figure 20: Anonymised GOSLON model and plaster models randomised and ready for scoring by each examiner.

Figure 21. Flow diagram to show the acquisition of dental models for the study population.



4.10.4 Ethical approval

Ethical approval was granted by the West of Scotland Ethics Service and Tayside Medical Centre for the assessment of a dental arch relationships in cleft care using impressions and an intraoral scanner (Chalmers, 2015)(Appendix V). Written and implied informed consent was required for each participating patient and where available, countersigned by parents up to the age of 18 years. Caldicott Guardian approval was granted by Glasgow and Greater Clyde National Health Service for the use of the digital models within the present study (Appendix VI). Ethical approval was not required for the investigation presented in this thesis as this project was an extension of the earlier work investigating dental arch relationships.

4.10.5 Funding

Funding was obtained through the Dundee Dental School Tattersall Research Fund for an educational license of the Rhino platform at a cost of €195.

4.11 Statistical analysis

4.11.1 Hypothesis testing

Descriptive statistics were used to quantitatively analyse the data. IBM SPSS Statistics package (V21.0) was used for the analysis (www-01.ibm.com/software/analytics/spss/products/statistics/).

- Hypothesis 1= MHB scores determined using the Rhino plug-in are no different to those determined using existing methods with Orthoanalyzer™ and plaster models.

MHB scores using conventional assessment on PLASTER models	MHB scores using conventional assessment on ORTHOANALYZER™ DIGITAL models	MHB scores using RHINO PLUG-IN
53 models of patients with UCLP	53 models of patients with UCLP	53 models of patients with UCLP
X 3 Examiners	X 3 Examiners	X 3 Examiners
2 Separate occasions	2 Separate occasions	2 Separate occasions

To test for agreement between the three model mediums Cronbach's alpha was used (Cronbach, 1951). Cronbach's alpha is a measure of internal consistency and was appropriate for the analysis of these data to show whether the three methods of scoring models were in agreement with each other. Alpha coefficients range from 0 to 1, where 1 describes total agreement of the variables under consideration, and 0 describes the inverse. An alpha coefficient of 0.7 has been suggested as an acceptable indicator of reliability (Nunnally,

1978) however, more detailed descriptors for Cronbach's alpha interpretation have been proposed (George and Mallery 2003)(Table 3).

Table 3. George and Mallery 2003, descriptors for Cronbach's Alpha

Cronbach Alpha value	**Internal consistency**
$\alpha \geq 0.9$	Excellent
$0.8 \leq \alpha < 0.9$	Good
$0.7 \leq \alpha < 0.8$	Acceptable
$0.6 \leq \alpha < 0.7$	Questionable
$0.5 \leq \alpha < 0.6$	Poor
$\alpha \leq 0.4$	Unreliable

4.11.2 Inter-observer and intra-observer reliability tests

Inter-observer and intra-observer reliability of the data was tested using Cronbach's alpha (Cronbach, 1951) and Intraclass Correlation Coefficients (Shrout and Fleiss, 1979) to test the level of agreement within data from the same observer and between observers.

- Hypothesis 2 = Measurements using the Rhino plug-in software are no different to those made on conventional plaster models.

Measurements were made for overbite (measured from the upper incisor erupted most) or anterior open bite (measured from the upper incisor erupted most), inter-canine width, inter-molar width, central incisor width (incisor chosen opposite side to the cleft) in mm with digital calipers to nearest 0.01mm, or using the Rhino distance measuring function.

Measurements in mm PLASTER	Measurements in mm DIGITAL
53 models	53 models
X 1 examiner	X 1 examiner
1 occasion	1 occasion

Descriptive statistics, a paired t-test and Bland-Altman plots were used for analysis of the data. A significance level of $p < 0.05$ was set. The paired t-test was chosen for this data as it facilitated analysis of any statistical differences between the two mediums. Bland-Altman plots (Bland and Altman, 1986) were again used for visual interpretation of outliers in the data and consistency of the data using 95% confidence intervals.

- Hypothesis 3 = The time taken to produce MHB scores using the Rhino plug-in is no different to using existing methods with digital and plaster models.

Clinical significance of the time difference between mediums was evaluated for these data.

4.11.3 Error Study

Digital landmarks were identified on 28 models on two separate occasions and tested for differences using paired t-test statistics, with a significance level $p<0.05$. Cronbach's alpha was also used to test agreement between the repeated measurements.

CHAPTER FIVE: RESULTS

5.1 Hypothesis 1

'MHB scores determined using the Rhino plug-in are no different to those determined using existing methods with digital and plaster models.'

Over the period of May 2015 to September 2015 a total of 53 plaster, digital and Rhino plug-in models were assessed by the three examiners, on two separate occasions under identical conditions. Total MHB scores and cumulative sores for the right buccal segment, left buccal segment and incisors were made on plaster and conventional digital models viewed in OrthoAnalyzer™. The same scores were computed using the Rhino plug-in (Appendix VII).

The data were examined for probability distribution using Skewness coefficients prior to statistical analysis. The data were found to follow a normal distribution. Cronbach's alpha (Cronbach, 1951) and Intraclass Correlation Coefficients (Koch, 1982) were used to determine the overall agreement between the three examiners for all variables scored (incisor MHB score, left side MHB score, right side score) across all mediums for the two data sets (Table 4 & 5).

Table 4. Cronbach's Alpha for combined examiner scores for all three mediums for all variables.

Medium	Cronbach's Alpha agreement
All mediums	0.986

Table 5. Intraclass correlation coefficients and confidence intervals for repeated scores from all examiners for all variables and all methods of scoring.

	Intraclass Correlation[b]	95% Confidence Interval	
		Lower Bound	Upper Bound
Single Measures	0.973[a]	0.971	0.975
Average Measures	0.986[c]	0.985	0.988

a. The estimator is the same, whether the interaction effect is present or not.
b. Type C intraclass correlation coefficients using a consistency definition- the between-measure variance is excluded from the denominator variance.
c. This estimate is computed assuming the interaction effect is absent, because it is not estimable otherwise.

This demonstrates excellent agreement between the examiners using the George and Mallery (2003) descriptors for Cronbach's Alpha interpretation. This indicates that the Rhino plug-in is no different to both plaster and conventional digital software for calculating MHB scores.

5.1.1 Inter-observer reliability

The agreement between the examiners for total MHB scores for each medium, (i.e. plaster, OrthoAnalyzer™ models and Rhino plug-in) was also calculated for the two data sets using Cronbach's Alpha and Intraclass Correlation coefficients (Table 6 & 7).

Table 6. Cronbach's Alpha for each medium used for repeated scores for the three examiners combined.

Medium	**Cronbach's Alpha agreement for Total MHB Scores**
Plaster	0.989
OrthoAnalyzer™	0.979
Rhino	0.991

Table 7. Intraclass correlation coefficients and confidence intervals for each medium using combined repeat scores, for all examiners for all variables.

Medium	Intraclass Correlation[b]	95% Confidence Interval	
		Lower Bound	Upper Bound
Single Measures Plaster	0.967[a]	0.954	0.976
Average Measures Plaster	0.989[c]	0.984	0.992
Single Measures OrthoAnalyzer™	0.938[a]	0.916	0.956
Average Measures OrthoAnalyzer™	0.979[c]	0.970	0.985
Single Measures Rhino	0.974[a]	0.965	0.982
Average Measures Rhino	0.991[c]	0.988	0.994

Two-way mixed effects model where people effects are random and measures effects are fixed.
a. The estimator is the same, whether the interaction effect is present or not.
b. Type C intraclass correlation coefficients using a consistency definition-the between-measure variance is excluded from the denominator variance.
c. This estimate is computed assuming the interaction effect is absent, because it is not estimable otherwise.

This also shows excellent agreement between all three examiners for the MHB total scores for each medium.

5.1.2 Intra-observer reliability

The intra-observer reliability was also calculated between the repeated scores from two separate occasions for the 53 models, for all variables (MHB score right, MHB incisors, MHB Left) using the three mediums (Table 8).

Table 8. Cronbach's Alpha for each examiner for repeated scores for all variables and mediums used for scoring.

Examiner	Cronbach's Alpha
1	0.988
2	0.987
3	0.986

Intraclass Correlation Coefficients (Koch, 1982) were also calculated as a measure of intra-observer reproducibility between the two MHB scores for each model on the two separate occasions (Table 9).

Table 9. Intraclass correlation coefficients and confidence intervals for each examiner for all variables and methods of scoring combined.

Examiner	Intraclass Correlation[b]	95% Confidence Interval	
		Lower Bound	Upper Bound
Single Measures 1	0.975[a]	0.971	0.979
Average Measures 1	0.988[c]	0.985	0.989
Single Measures 2	0.974[a]	0.970	0.978
Average Measures 2	0.987[c]	0.985	0.989
Single Measures 3	0.972[a]	0.967	0.976
Average Measures 3	0.986[c]	0.983	0.988

Two-way mixed effects model where people effects are random and measures effects are fixed.
a. The estimator is the same, whether the interaction effect is present or not.
b. Type C intraclass correlation coefficients using a consistency definition-the between-measure variance is excluded from the denominator variance.
c. This estimate is computed assuming the interaction effect is absent, because it is not estimable otherwise.

The results show that there was excellent intra-observer agreement between the examiners demonstrating that each examiner was consistent with repeated scoring.

Bland-Altman (Bland and Altman, 1986) plots were then created for visual interpretation of the repeatability of MHB total scores for plaster models, OrthoAnalyzer™ models and the Rhino plug-in for the three examiners (Figure 22). These plots were useful to identify any systematic bias and indentify any data outliers. A 95% confidence interval was set which can be described as the mean difference of the two readings plus or minus 1.96 times the standard deviation of the differences.

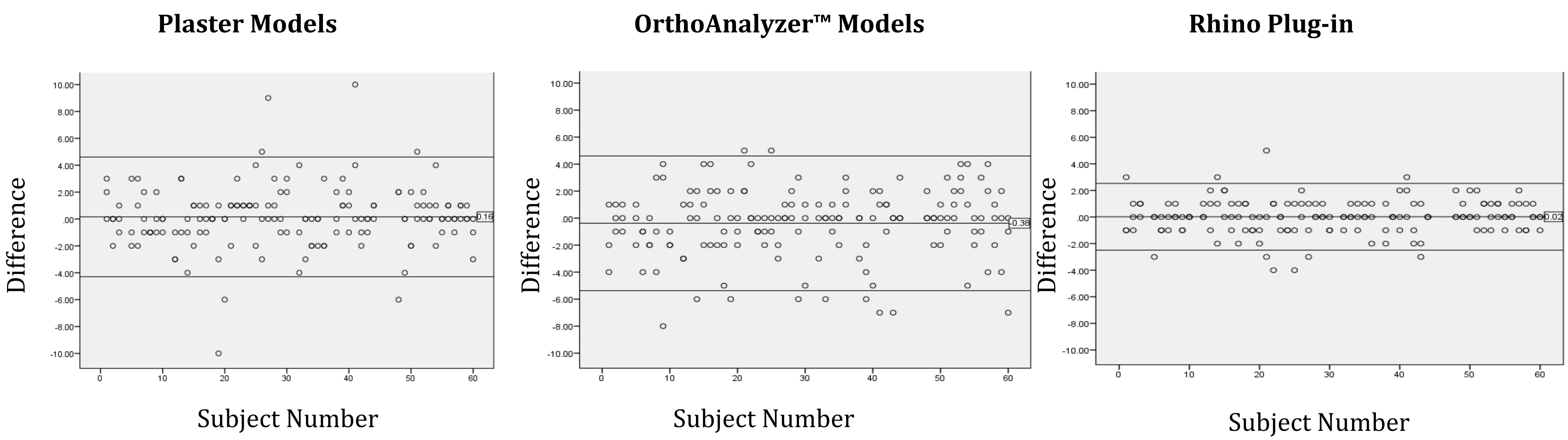


Figure 22. Bland-Altman plots for Total MHB scores for all examiners with different mediums.

These plots show that the majority of the data for the three examiners for the three mediums lies between the upper and lower confidence intervals with a good scatter of points around the mean difference of the two readings. However, these highlight that there are more data points for the OrthoAnalyzer™ digital models total MHB scores that lie beyond the confidence intervals than with the plaster and Rhino plug-in total MHB scores, highlighting more outliers. These plots also highlight the smaller confidence intervals for the Rhino Software tool, suggesting that the Rhino plug-in is more consistent for scoring than the other two mediums.

As there was excellent agreement between the methods for all variables and excellent intra and inter examiner repeatability, the first null hypothesis that MHB scores determined using the novel software program are no different to the existing calculation of MHB scores using digital and plaster models was accepted.

5.2 Hypothesis 2

'Measurements using the Rhino plug-in software are no different to those made on conventional plaster models. '

Inter-canine, inter-molar, overbite/anterior open bite and the width of the central incisor were measured for the 53 digital and plaster models of patients with UCLP. The measurements made in Rhino were compared to the 'gold standard' measurements from plaster models. Descriptive statistics were used along with a paired t-test (Table 10).

Table 10. Descriptive statistics and paired t-test for differences between measurements made in millimeters using the Rhino software tool and digital calipers on plaster models.

Parameter measured	N	Minimum	Maximum	Mean	Std. Deviation	Significance (2-tailed)
Overbite Plaster	52	-3.83	7.62	2.14	2.31	
Overbite Rhino	52	-3.61	7.88	2.47	2.22	0.019*
Inter-canine width Max Plaster	53	14.62	35.77	26.89	4.83	
Inter-canine width Max Rhino	53	17.24	36.67	27.28	4.77	0.060
Inter-molar width Max Plaster	53	34.00	50.83	42.16	3.71	
Inter-molar width Max Rhino	53	33.44	50.36	42.21	3.64	0.731
Inter-canine width Man Plaster	53	21.04	29.15	25.40	1.92	
Inter-canine width Man Rhino	53	21.14	29.34	25.57	1.81	0.122
Inter-molar width Man Plaster	53	33.57	49.83	40.59	3.43	
Inter-molar width Man Rhino	53	34.64	50.49	41.03	3.45	0.003*
Width Max Inc Plaster	52	6.51	10.07	8.08	0.70	
Width Max Inc Rhino	52	6.22	10.16	8.09	0.75	0.832

* The mean difference is significant at $p<0.05$. Max= Maxillary, Man= Mandibular, Inc= incisor, 1= first data collection readings, 2=second data collection readings.

The descriptive statistical data shows that the means for the two methods of measurement are very similar. Only 52 readings could be made for overbite and width of the upper central incisor as one model did not have any central incisors, thus measurements could not be recorded for this model.

A paired t-test was chosen for these data as it facilitated analysis of any statistical differences between the two mediums. Statistical significance was found for readings between the overbite and inter-molar widths of the mandibular model with p values of 0.019 and 0.003 respectively. However, examination of the paired mean difference for measurements of overbite was 0.33mm and 0.44 mm for inter-molar width, which is not considered to be clinically significant. Clinical significance would be considered for small measurements such as overbite if >0.5mm and for transverse measurements >1mm.

Bland-Altman plots were constructed to show the differences between the two measurement methods scattered about the mean (Figure 23 & 24).

A. Overbite measurements

B. Maxillary inter-canine width measurements

C. Maxillary inter-molar width measurements

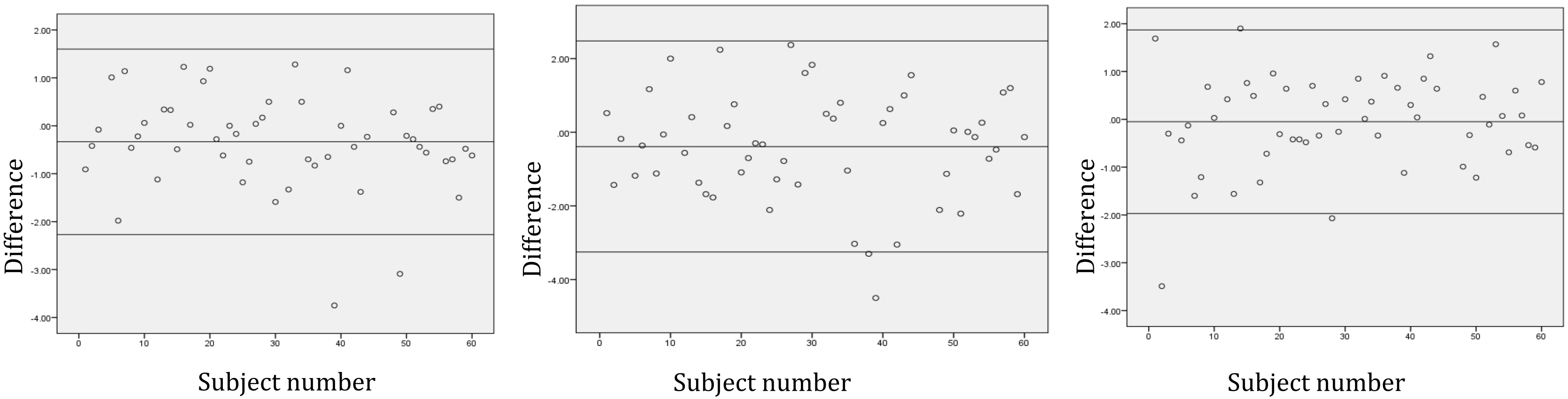
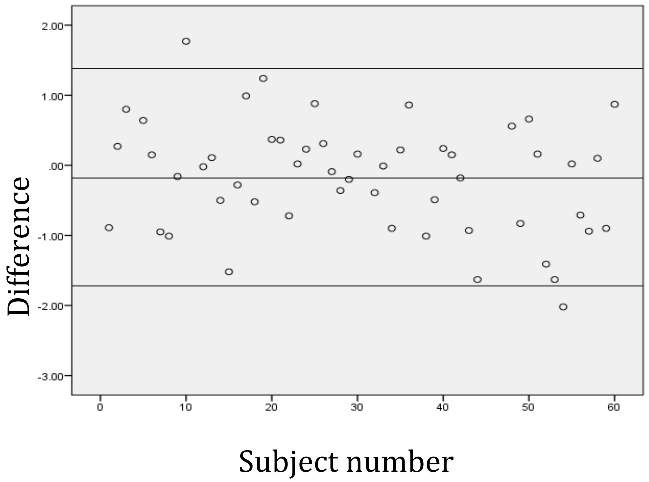
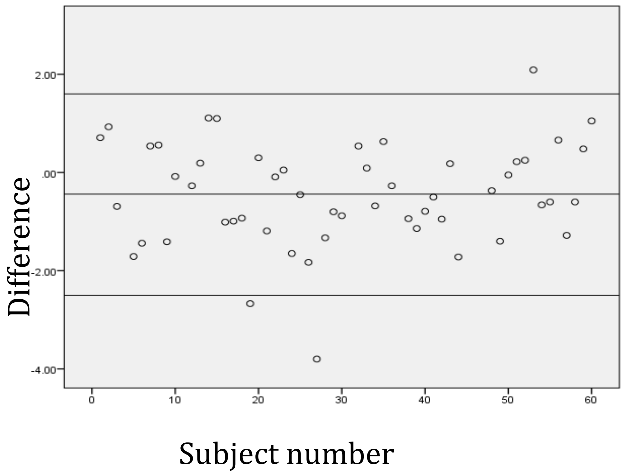


Figure 23. Bland-Altman plots for a single examiner for each parameter measured in millimeters. A. Overbite B. Maxillary inter-canine width. C. Maxillary inter-molar width. D. Mandibular inter-canine width. E. Mandibular inter-molar width. F. Central incisor width.

D. Mandibular inter-canine width measurements



E. Mandibular inter-molar width measurements



F. Central incisor width measurements

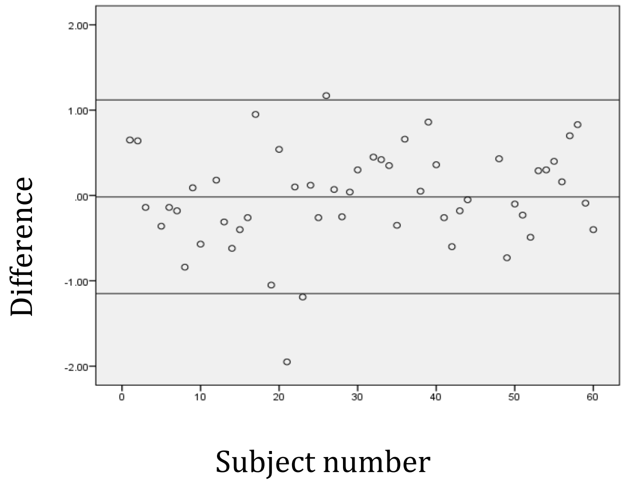


Figure 24. Bland-Altman plots for all examiners combined for each parameter measured in millimeters. A. Overbite B. Maxillary inter-canine width. C. Maxillary inter-molar width. D. Mandibular inter-canine width. E. Mandibular inter-molar width. F. Central incisor width.

The plots show that there is a good degree of scatter around the mean difference separating the Rhino and plaster measurements between the confidence intervals set at 95%. This confirms that the Rhino software is a reliable method of recording measurements.

5.2.1 Intra-observer reliability

To ensure the reliability of the new method of calculating measurements in the Rhino plug-in software, repeat measurements were made for 28 models on both plaster models and models in Rhino. A paired sample t-test was used to calculate any significant differences between the two readings ($p < 0.05$) (Table 11). Repeatability coefficients were calculated for both mediums.

Table 11. Descriptive statistics and paired t-test for differences between measures made in millimeters using digital calipers on plaster models.

Parameter and measurement episode	Mean	N	Std. Deviation	Std. Error Mean	Significance (2-tailed)
Overbite 1	1.94	27	2.52	0.48	
Overbite 2	2.10	27	2.55	0.49	0.065
Inter-canine width Max 1	26.18	28	4.49	0.85	
Inter-canine width Max 2	26.23	28	4.60	0.87	0.709
Inter-molar width Max 1	41.38	28	3.57	0.68	
Inter-molar width Max 2	41.27	28	3.67	0.69	0.319
Inter-canine width Man 1	25.24	28	2.13	0.40	
Inter-canine width Man 2	25.17	28	1.95	0.37	0.555
Inter-molar width Man 1	40.08	28	2.80	0.53	
Inter-molar width Man 2	39.45	28	2.77	0.53	0.000*
Width Max Inc 1	8.01	27	0.76	0.15	
Width Max Inc 2	8.07	27	0.70	0.13	0.226

* The mean difference is significant at $p<0.05$. Max= Maxillary, Man= Mandibular, Inc= incisor, 1= first data collection readings, 2= second data collection readings.

The descriptive statistics show no clinically significant differences in the means between the two measurements. (Note for overbite and the width of the upper central incisor, there are only 27 repeat measurements as one model did not have any upper incisors.) The only parameter with statistical significance is the difference between the inter-molar width in the mandibular model (p=0.000).

However, when paired differences between the mean for this parameter were assessed, the value was 0.63 mm, which was not clinically significant.

Table 12. Descriptive statistics and paired t-test for differences between measurements made in millimeters using the Rhino software tool.

Parameter and measurement episode	Mean	N	Std. Deviation	Std. Error Mean	Significance (2-tailed)
Overbite 1	2.06	27	2.28	0.44	
Overbite 2	1.89	27	2.30	0.44	0.012*
Inter-canine width Max 1	26.49	28	4.46	0.84	
Inter-canine width Max 2	26.40	28	4.44	0.84	0.523
Inter-molar width Max 1	41.59	28	3.35	0.63	
Inter-molar width Max 2	41.69	28	3.56	0.67	0.501
Inter-canine width Man 1	25.20	28	1.86	0.35	
Inter-canine width Man 2	25.33	28	1.81	0.34	0.123
Inter-molar width Man 1	40.71	28	2.77	0.52	
Inter-molar width Man 2	40.56	28	2.74	0.52	0.254
Width Max Inc 1	8.14	27	0.69	0.13	
Width Max Inc 2	8.00	27	0.61	0.12	0.318

* The mean difference is significant at $p<0.05$. Max= Maxillary, Man= Mandibular, Inc= incisor, 1= first data collection readings, 2= second data collection readings.

The descriptive statistics for the means for the repeat measurements demonstrated a low level of clinical difference (Table 12). The t-test found that only the overbite was statistically significant ($p=0.012$), unlike the plaster measurements where significant differences for inter-molar width were noted.

The paired difference between the mean for overbite measured in the Rhino software was 0.17 mm, which was not clinically significant.

Repeatability coefficients (BritishInstitution, 1979) were determined for repeat measurements for the six parameters for both the measurements made using conventional plaster models and the Rhino plug-in software. Repeatability coefficients are a useful tool to give absolute reliability in the same units as the measurement tool (Vaz et al., 2013), for repeated measurements on the same subject. The units for this data were measured in millimeters. In this analysis it was used to provide the difference in measurements up to approximately 2 standard deviations between repeat measurements made on either plaster or Rhino plug-in models with 95% confidence.

Parameter pairs between measurement episodes	Repeatability coefficients Plaster	Repeatability coefficients Rhino
Overbite 1 – Overbite 2	0.81	0.64
Inter-canine width Max 1 – Inter-canine width Max 2	1.16	1.47
Inter-molar width Max 1 – Inter-molar width Max 2	1.06	1.55
Inter-canine width Man 1 – Inter-canine width Man 2	1.25	0.86
Inter-molar width Man 1 – Inter-molar width Man 2	1.42	1.40
Width Max Inc 1 – Width Max Inc 2	0.53	1.41

Max= Maxillary, Man= Mandibular, Inc= incisor, 1= first data collection readings, 2= second data collection readings.

Table 13. Repeatability coefficients for measurements of absolute reliability between measurements made in millimeters using the Rhino plug-in software measuring tool and digital calipers on plaster models.

The results demonstrate slightly lower repeatability coefficients for plaster over Rhino plug-in models for maxillary inter-canine and inter-molar widths, and the widths of the upper central incisors. The inverse is true for inter-canine and inter-molar widths for the mandibular model and overbite. The biggest difference exists between plaster and Rhino plug-in repeatability coefficients for the widths of the central incisors. Overall, the repeatability coefficients for the two mediums were less than 1.6mm, which is clinically insignificant, particularly for inter-canine and inter-molar widths, and are generally similar between the two mediums.

Taking all of the data into consideration, there was good correlation between the two sets of measurements made using the Rhino software tool and the measurements on plaster models. Although statistical differences were highlighted for overbite and mandibular inter-molar width, these differences were not regarded as clinically significant. There was good repeatability of the two measurements, and this was demonstrated with the repeatability coefficients. This means that the second null hypothesis, that measurements made using the software platform used to develop the MHB software tool are no different to the measurements made on conventional plaster models, was accepted.

5.3 Error study

A paired t-test and Cronbach's alpha were used to compare the reliability of repeated Cartesian co-ordinates for 28 digital models on two separate occasions (Table 14). An x, y and z variable was identified for each of the digital landmarks used for development of the novel software to test for consistency of landmark identification.

A. Overbite measurements

B. Maxillary inter-canine width measurements

C. Maxillary inter-molar width measurements

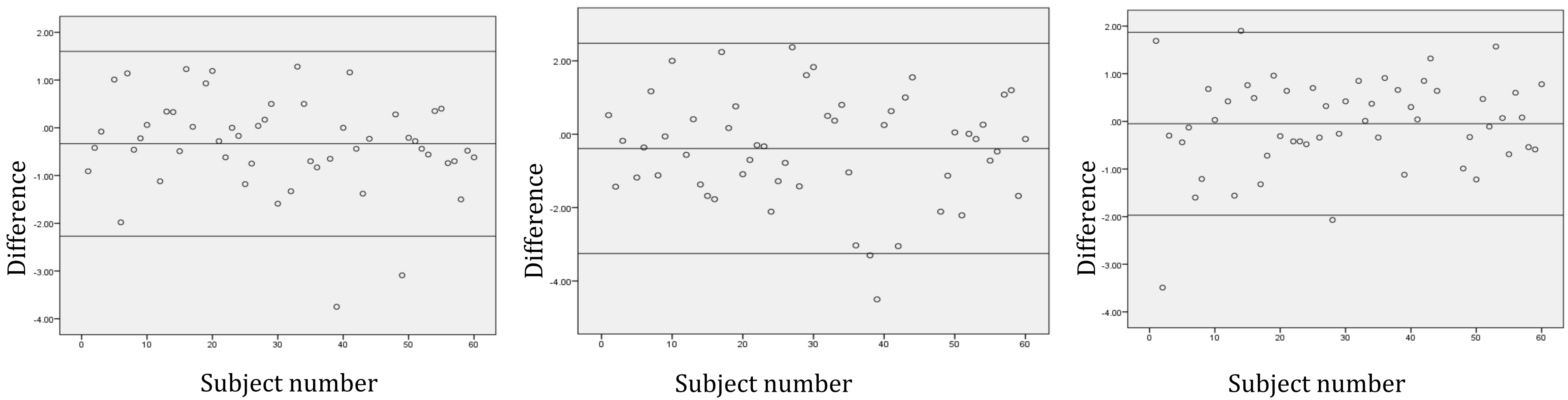
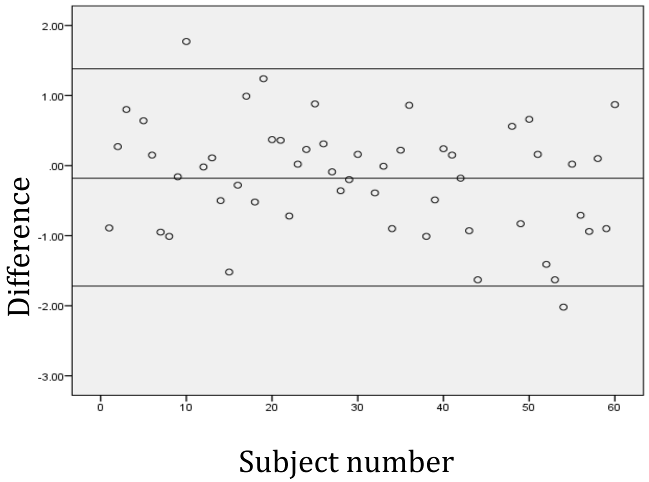
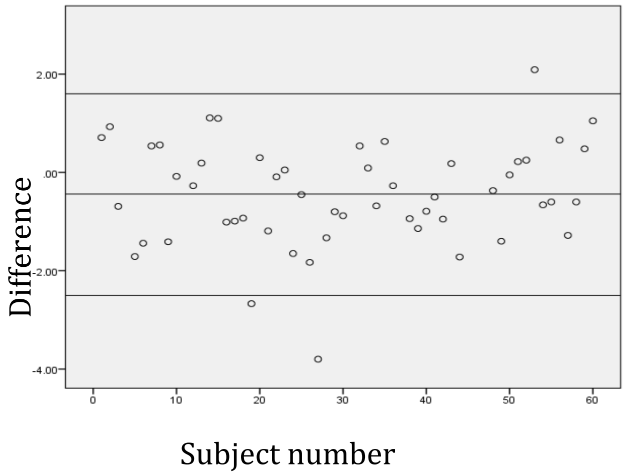


Figure 23. Bland-Altman plots for a single examiner for each parameter measured in millimeters. A. Overbite B. Maxillary inter-canine width. C. Maxillary inter-molar width. D. Mandibular inter-canine width. E. Mandibular inter-molar width. F. Central incisor width.

D. Mandibular inter-canine width measurements



E. Mandibular inter-molar width measurements



F. Central incisor width measurements

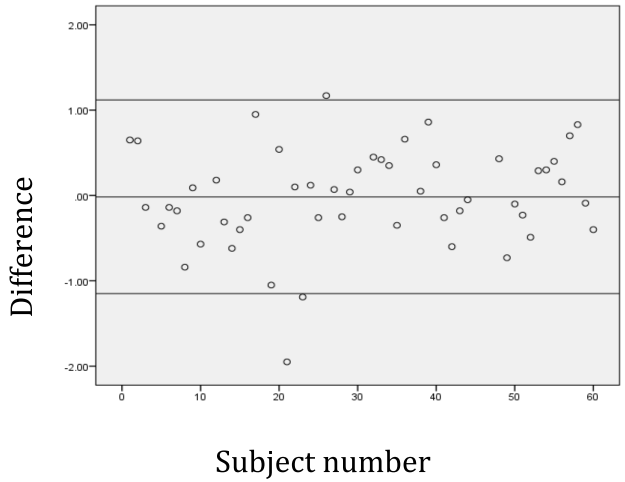


Figure 24. Bland-Altman plots for all examiners combined for each parameter measured in millimeters. A. Overbite B. Maxillary inter-canine width. C. Maxillary inter-molar width. D. Mandibular inter-canine width. E. Mandibular inter-molar width. F. Central incisor width.

The plots show that there is a good degree of scatter around the mean difference separating the Rhino and plaster measurements between the confidence intervals set at 95%. This confirms that the Rhino software is a reliable method of recording measurements.

5.2.1 Intra-observer reliability

To ensure the reliability of the new method of calculating measurements in the Rhino plug-in software, repeat measurements were made for 28 models on both plaster models and models in Rhino. A paired sample t-test was used to calculate any significant differences between the two readings ($p < 0.05$) (Table 11). Repeatability coefficients were calculated for both mediums.

Table 11. Descriptive statistics and paired t-test for differences between measures made in millimeters using digital calipers on plaster models.

Parameter and measurement episode	Mean	N	Std. Deviation	Std. Error Mean	Significance (2-tailed)
Overbite 1	1.94	27	2.52	0.48	
Overbite 2	2.10	27	2.55	0.49	0.065
Inter-canine width Max 1	26.18	28	4.49	0.85	
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Inter-canine width Man 1	25.24	28	2.13	0.40	
Inter-canine width Man 2	25.17	28	1.95	0.37	0.555
Inter-molar width Man 1	40.08	28	2.80	0.53	
Inter-molar width Man 2	39.45	28	2.77	0.53	0.000*
Width Max Inc 1	8.01	27	0.76	0.15	
Width Max Inc 2	8.07	27	0.70	0.13	0.226

* The mean difference is significant at $p<0.05$. Max= Maxillary, Man= Mandibular, Inc= incisor, 1= first data collection readings, 2= second data collection readings.

The descriptive statistics show no clinically significant differences in the means between the two measurements. (Note for overbite and the width of the upper central incisor, there are only 27 repeat measurements as one model did not have any upper incisors.) The only parameter with statistical significance is the difference between the inter-molar width in the mandibular model (p=0.000).

However, when paired differences between the mean for this parameter were assessed, the value was 0.63 mm, which was not clinically significant.

Table 12. Descriptive statistics and paired t-test for differences between measurements made in millimeters using the Rhino software tool.

Parameter and measurement episode	Mean	N	Std. Deviation	Std. Error Mean	Significance (2-tailed)
Overbite 1	2.06	27	2.28	0.44	
Overbite 2	1.89	27	2.30	0.44	0.012*
Inter-canine width Max 1	26.49	28	4.46	0.84	
Inter-canine width Max 2	26.40	28	4.44	0.84	0.523
Inter-molar width Max 1	41.59	28	3.35	0.63	
Inter-molar width Max 2	41.69	28	3.56	0.67	0.501
Inter-canine width Man 1	25.20	28	1.86	0.35	
Inter-canine width Man 2	25.33	28	1.81	0.34	0.123
Inter-molar width Man 1	40.71	28	2.77	0.52	
Inter-molar width Man 2	40.56	28	2.74	0.52	0.254
Width Max Inc 1	8.14	27	0.69	0.13	
Width Max Inc 2	8.00	27	0.61	0.12	0.318

* The mean difference is significant at $p<0.05$. Max= Maxillary, Man= Mandibular, Inc= incisor, 1= first data collection readings, 2= second data collection readings.

The descriptive statistics for the means for the repeat measurements demonstrated a low level of clinical difference (Table 12). The t-test found that only the overbite was statistically significant ($p=0.012$), unlike the plaster measurements where significant differences for inter-molar width were noted.

The paired difference between the mean for overbite measured in the Rhino software was 0.17 mm, which was not clinically significant.

Repeatability coefficients (BritishInstitution, 1979) were determined for repeat measurements for the six parameters for both the measurements made using conventional plaster models and the Rhino plug-in software. Repeatability coefficients are a useful tool to give absolute reliability in the same units as the measurement tool (Vaz et al., 2013), for repeated measurements on the same subject. The units for this data were measured in millimeters. In this analysis it was used to provide the difference in measurements up to approximately 2 standard deviations between repeat measurements made on either plaster or Rhino plug-in models with 95% confidence.

Parameter pairs between measurement episodes	Repeatability coefficients Plaster	Repeatability coefficients Rhino
Overbite 1 – Overbite 2	0.81	0.64
Inter-canine width Max 1 – Inter-canine width Max 2	1.16	1.47
Inter-molar width Max 1 – Inter-molar width Max 2	1.06	1.55
Inter-canine width Man 1 – Inter-canine width Man 2	1.25	0.86
Inter-molar width Man 1 – Inter-molar width Man 2	1.42	1.40
Width Max Inc 1 – Width Max Inc 2	0.53	1.41

Max= Maxillary, Man= Mandibular, Inc= incisor, 1= first data collection readings, 2= second data collection readings.

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The results demonstrate slightly lower repeatability coefficients for plaster over Rhino plug-in models for maxillary inter-canine and inter-molar widths, and the widths of the upper central incisors. The inverse is true for inter-canine and inter-molar widths for the mandibular model and overbite. The biggest difference exists between plaster and Rhino plug-in repeatability coefficients for the widths of the central incisors. Overall, the repeatability coefficients for the two mediums were less than 1.6mm, which is clinically insignificant, particularly for inter-canine and inter-molar widths, and are generally similar between the two mediums.

Taking all of the data into consideration, there was good correlation between the two sets of measurements made using the Rhino software tool and the measurements on plaster models. Although statistical differences were highlighted for overbite and mandibular inter-molar width, these differences were not regarded as clinically significant. There was good repeatability of the two measurements, and this was demonstrated with the repeatability coefficients. This means that the second null hypothesis, that measurements made using the software platform used to develop the MHB software tool are no different to the measurements made on conventional plaster models, was accepted.

5.3 Error study

A paired t-test and Cronbach's alpha were used to compare the reliability of repeated Cartesian co-ordinates for 28 digital models on two separate occasions (Table 14). An x, y and z variable was identified for each of the digital landmarks used for development of the novel software to test for consistency of landmark identification.

Table 14. A paired t-test for analysis of significant differences between x, y and z variables.

Tooth and measurement episode	Paired Differences					Significance (2-tailed)
	Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference		
				Lower	Upper	
UL6.1 - UL6.2	0.33	3.28	0.36	-0.38	1.05	0.352
UL5.1 - UL5.2	0.37	2.72	0.30	-0.22	0.96	0.220
UL4.1 - UL4.2	0.29	1.74	0.19	-0.08	0.67	0.124
UL3.1 - UL3.2	0.27	1.76	0.19	-0.11	0.65	0.161
UL1.1 - UL1.2	0.14	1.39	0.15	-0.16	0.44	0.364
UR1.1 - UR1.2	0.08	0.61	0.07	-0.05	0.21	0.246
UR3.1 - UR3.2	-0.40	2.32	0.25	-0.90	0.11	0.122
UR4.1 - UR4.2	-0.21	1.78	0.19	-0.60	0.18	0.282
UR5.1 - UR5.2	-0.23	2.07	0.23	-0.68	0.22	0.320
UR6.1 - UR6.2	-0.23	2.42	0.26	-0.75	0.30	0.388
LR6.1 - LR6.2	-0.21	1.81	0.20	-0.60	0.19	0.295
LR5.1 - LR5.2	-.071	3.58	0.39	-1.49	0.07	0.072
LR4.1 - LR4.2	-0.42	2.64	0.29	-0.99	0.16	0.153
LR3.1 - LR3.2	-.013	1.20	0.13	-0.40	0.12	0.299
LR2.1 - LR2.2	-0.14	0.84	0.09	-0.32	0.05	0.143
LR1.1 - LR1.2	-0.08	0.45	0.05	-0.18	0.02	0.105
LL1.1 - LL1.2	0.01	0.24	0.03	-0.04	0.07	0.595
LL2.1 - LL2.2	0.11	0.98	0.11	-0.10	0.32	0.312
LL3.1 - LL3.2	0.18	1.73	0.19	-0.19	0.56	0.330
LL4.1 - LL4.2	0.28	2.35	0.26	-0.23	0.79	0.273

Table 14. A paired t-test for analysis of significant differences between x, y and z variables CONTINUED.

LL5.1 - LL5.2	0.30	2.61	0.28	-0.27	0.86	0.300
LL6.1 - LL6.2	0.41	3.16	0.35	-0.28	1.11	0.241

* The mean difference is significant at $p<0.05$. 1= fist data collection readings, 2=second data collection readings.

These data show there were no significant differences between the x, y, and z variables combined for any anatomical landmark. Cronbach's alpha was calculated for the 22 pairs to calculate a combined single value for x, y and z variables (Table 15).

Table 15. Cronbach's Alpha for repeat measurements made for x, y and z variables combined.

Cronbach's Alpha	N of Items
0.933	44

The value obtained using this statistical method showed an excellent internal consistency between the two samples.

5.4 Hypothesis 3

'The time taken to produce MHB scores using the Rhino plug-in is no different to using existing methods with digital and plaster models.'

The chief investigator recorded the total time taken to score the MHB scores for all 53 models, using plaster, OrthoAnalyzer™ models and the Rhino plug-in (Table 16).

Table 16. Time taken to score MHB on different model mediums.

Medium for MHB scoring	Time taken in minutes & seconds
Plaster	55.40
Digital	64.16
Rhino software tool	235.55

There was a clinically significant difference between the time required for the Rhino plug-in and the two conventional methods of scoring MHB scores. The results demonstrate the Rhino plug-in takes approximately 4 times longer than conventional methods. Therefore the third hypothesis, that there is no difference in the time taken to produce MHB scores between the Rhino plug-in and existing methods of scoring, is rejected.

CHAPTER SIX: DISCUSSION

6.1 Hypothesis 1

'MHB scores determined using the Rhino plug-in are no different to those determined using existing methods with digital and plaster models.'

Excellent agreement was found between all the examiners for MHB scoring for all three model mediums (plaster, OrthoAnalyzer™ and Rhino plug-in models) (George, 2003). It has been suggested that greater than 0.9 should be regarded as the appropriate threshold for clinical application (Bland and Altman, 1997), which all of the three mediums exceeded. Furthermore, there was excellent agreement between the examiners for each scoring medium. Whilst the highest level of agreement was found for the Rhino plug-in (0.991), followed closely by plaster models (0.989), OrthoAnalyzer™ models had the lowest, but still an excellent level of agreement (0.979) (Table 6). The Rhino plug-in also had the narrowest confidence intervals for all three methods. This is shown on the Bland Altman plots where the consistency of the data has a greater concentration around the mean (Figure 22). This indicates the new automated system, despite in its infancy, is as effective, if not more accurate, than existing methods of MHB scoring. Overall the data reveals the excellent agreement with the existing scoring systems enabling the null hypothesis to be accepted.

6.1.1 Outliers

The Bland-Altman plots enabled visualisation of any systematic bias, the consistency of the data and any outliers. For each subject, the three mediums demonstrated a good scatter of the data on, and about the mean, with the majority of the data being within the 95% confidence intervals. However, there were several outliers. Within the plaster model data set there were 7 data points sited outside the confidence intervals, while for the OrthoAnalyzer™ model data set and the Rhino plug-in there were 11 and 9 data points, respectively outside the confidence intervals. The y-axis scale for each plot refers to the difference from the mean for each data subject. As this was calibrated to be the same scale for each medium, this highlights the narrower confidence interval for the Rhino plug-in over the two existing methods of scoring.

The significant outliers were examined further to account for any anomalies in the occlusion of the study participant that could influence the data. Plaster model subjects 19, 27 and 41 had the greatest variance from the mean difference in MHB scoring. Subject 19 had an MHB difference of 10 between first and second readings for examiner three. Subject 27 had an MHB difference of 9 and subject 41 had a difference of 10, both recorded between first and second readings by examiner one. Examination of malocclusion types for these subjects revealed subject 19 had a class II/I incisor malocclusion with an increased overjet. Subject 27 and 41 had significant class III malocclusions, both with difficult occlusal registrations, however one had a deep overbite, while the other had an anterior open bite. This suggests differences maybe attributable to random errors in scoring rather than specific malocclusion types.

The MHB scores for the OrthoAnalyzer™ models showed significant outliers for subjects 9, 41, 43 and 60. Subject 9 had an MHB difference of 8 between readings by examiner three. Subject 41 a difference of 7 by examiner one, subject 43 a difference of 7, and subject 60 a difference of 8, the latter two by examiner three. The occlusion types for these subjects displayed a mixture of both class III and II/I incisor malocclusions, ranging from extensive crossbites to those with good alignment.

The Rhino plug-in MHB scores had significant outliers for subjects 21, 22 and 25. Subject 21 had a difference of 5 between readings by examiner one, while subjects 22 and 25 had differences of 4 by examiner two. Interestingly a difference of four in MHB scoring would not have been considered an outlier on the Bland-Altman plots with plaster or OrthoAnalyzer™ models. This demonstrates the consistency using the Rhino-plug-in to produce accurate scores, even when used by examiners unfamiliar with this scoring method. All of the outliers produced, using this method of scoring, were for subjects with class III malocclusions and varying degrees of crossbite discrepancy. This suggests that these outliers were more consistent with random errors. All three examiners contributed to the outliers for all three mediums, therefore these errors are not the responsibility of a single examiner.

Outliers in data can be caused by a number of factors. Landmark misidentification can lead to significant errors in scoring, as well as recording errors, and human errors. As the Rhino plug-in is a more objective system, human error associated with outliers is minimised, which could explain the results. At present, landmark identification is required with all of the methods of scoring and this is subject to both random and systematic bias (this has the potential to be eliminated with integration of software recognition functions into the Rhino plug-in (Section 6.12.2*: User-friendly adaptation*). However, aspects such as score recording and subjective choosing of an MHB score for each pair of teeth are eliminated with the Rhino plug-in software. Furthermore, maxillary and mandibular models within the software are registered with an occlusal registration that is not changeable between the first and second data recordings. Plaster models are more difficult to register occlusally when there is an anterior open bite or a class III malocclusion, which is likely in our subject sample. Therefore manual manipulation of the plaster models between readings could result in varying occlusions on different occasions, thereby affecting the MHB scores and leading to a greater number of outliers.

6.1.2 Surgical outcomes in previous studies

Much of the research in the field investigating surgical outcomes in clefting deformities has been focused on establishing methods of assessment for 2D images or 3D digital model images against plaster models using subjective scoring methods such as the GOSLON Yardstick, 5 year old index and BCLP Yardstick (Nollet et al., 2004, McAuliffe et al., 2011, Bartzela et al., 2011). As this Rhino plug-in has not been previously investigated or validated, comparisons can only be drawn to existing methods of assessment and the few studies using the more objective MHB scoring systems outlined previously.

A recent study comparing manual MHB scoring using plaster digital models, OrthoAnalyzer™ digital models and models produced from intraoral scanning found similar findings, using Cronbach's alpha to examine agreement between examiners. Plaster, OrthoAnalyzer™ and direct digital models were found to have excellent agreement levels at 0.988, 0.984 and 0.990 respectively (Chalmers, 2015). Although the results for plaster and OrthoAnalyzer™ digital models are comparable, in this present study direct digital models from intraoral scans were not investigated, therefore future work could investigate the use of the Rhino-plug in with direct digital models. Taking the results into account with the data presented by Chalmers (2015), a good level of agreement would be expected.

Other studies investigating surgical outcome scoring in patients with UCLP have found good to very good inter-observer agreement between plaster and indirect digital models (Chawla et al., 2013), produced from scanned plaster models. This study found the weighted Kappa values ranged from 0.83 to 0.87 for plaster models and 0.74 to 0.83 for the indirect digital models. The slightly lower agreement between examiners with the digital models compared with plaster is comparable with the findings of the current research, however the study used the 5 year old index which is a more subjective scoring system for CL/P. Comparisons are therefore limited.

Studies that have compared plaster to digital models, using the MHB system in patients with UCLP have found no significant differences between plaster and digital models (Asquith and McIntyre, 2012). Inter-observer reproducibility was good or very good (0.64 to 0.78) with weighted Kappa values. A similar level of intra-observer consistency was found. However, the small study sample of 30 was a weakness of this study.

6.2 Hypothesis 2

'Measurements using the Rhino plug-in software are no different to those made on conventional plaster models. '

Mean differences between the measurements made using the Rhino plug-in and plaster models were found to be similar. Statistical significance was found to exist for overbite measurements and inter-molar widths for mandibular models ($p<0.05$). When the paired differences between the means were examined, differences were 0.33mm for overbite and 0.44mm for mandibular inter-molar width. These values are small and unlikely to be clinically significant. Other studies have found that digital models produce comparable measurement discrepancies when compared to plaster (Fleming et al., 2011). In the systematic review by Fleming and co-authors, four studies were found to compare differences between the two mediums in the transverse dimension. Investigating the inter-canine, inter-molar and inter-premolar distances collectively the mean discrepancies ranged from 0.04 to 0.4mm, which were not considered significant (Fleming et al., 2011).

Overbite has been found to be statistically significantly different in other studies comparing plaster models to digital models. Differences of 0.49mm and 0.27mm, have been observed and regarded as clinically insignificant (Stevens et al., 2006, Santoro et al., 2003, Quimby et al., 2004). In these studies the mean overbite measurements on digital models were smaller than the plaster measurements, which is contrary to the results of this study. For plaster models the mean overbite measurements were 2.14mm. For the Rhino plug-in this was 2.47mm, resulting in an average difference of 0.33mm. It has been suggested that overbite differences are subject to variations in the viewing perspective when recording this measurement (Santoro et al., 2003). Other factors that may contribute are incorrect handling and difficulties in the measurement of anterior open bite and reverse overjets. These malocclusion types were particularly prevalent in this study sample due to the nature of the deformities present. This may lead to increased human error in recording overbite, especially for plaster models where maintaining a fixed occlusal registration for the models can be a challenge when trying to take readings with digital calipers. Human error has previously been reported to be approximately 0.2mm in repeated clinical measurements for plaster models (Santoro et al., 2000).

Differences in transverse arch dimensions between digital and plaster models have been reported to be <0.38mm (De Luca Canto et al., 2015). In this study a difference was noted to be on average 0.44mm between the two mediums. Subtle differences in the mean for inter-molar measurements leading to statistical significance could also be attributed to subtle differences in the viewing perspective of the digital models when compared to the plaster. In addition, inaccuracies in landmark identification of the inter-molar fossae with digital models may also have a role. During the study it was noted that some of the detail on the digital models had been lost when compared to plaster models. This made the precise location of the inter-molar fossae difficult to detect. When taking into account the distance over which the measurement is made for mandibular inter-molar width (40.59mm for plaster and 41.03mm Rhino) a 0.44mm discrepancy (around 1%) was deemed not to be clinically significant.

Proffit quoted values of 1.5mm to be clinically insignificant for tooth size discrepancy measurements (Proffit et al., 2014). With this in mind, repeated measurements on plaster models for mandibular inter-molar width were shown to be statistically significant ($p<0.05$), with the differences between the means of 0.62mm. For measurements made using the Rhino software, overbite was found to be statistically significantly different to the measurement from plaster models ($p=0.012$), with the difference between the means of 0.17mm. Again these differences in the means were considered not to be clinically significant. Repeatability coefficients were an excellent method to demonstrate the degree of accuracy associated with either the manual or digital measurement method. For the two methods, plaster was more accurate for maxillary inter-canine and inter-molar width, mandibular inter-canine width and the width of a central incisor. The digital software was more accurate for overbite and mandibular inter-canine widths. However, the small differences between the repeatability coefficients are again unlikely to be of significance for a clinical application.

6.2.1 Outliers

There are significant outliers for each of the measurement parameters between readings made with Plaster and Rhino models. Overbite measurements showed outliers for subjects 39 and 49 with differences of 3.75mm and 3.09mm respectively. Examination of these model types showed 39 to have an average overbite while 49 to have a deep overbite. No obvious cause could be attributed to the significant differences. It is proposed that either the models were not in centric occlusion when viewing with plaster models, or inaccurate location of the control points when measuring overbite with the Rhino software measuring tool were responsible. Maxillary inter-canine widths had a single outlier for model 39 with a difference of 4.5mm. This subject was in the mixed dentition, with an unusually placed UL3 and a partially erupted UR3. This is a potential for landmark identification error, and was unusual compared to the rest of the subjects.

Subject 2 for maxillary inter-molar width had an outlier with a difference of 3.49mm between the plaster and the Rhino software. This subject had clinically significant maxillary arch constriction due to the clefting defect. Molars were also rotated with occlusal restorations precluding an accurate assessment of the occlusal fossae. This could have made landmark identification in the molars difficult for recording molar widths.

Mandibular intercanine width had a clinically significant outlier for subject 10, where the differences in measurement equated to a difference of 1.77mm. This subject had good occlusal detail and mild anterior crowding. No specific reason could be attributed to this outlier other than random landmark identification bias. This is also true for the mandibular intermolar outlier for subject 27, who had a difference of 3.80mm. This subject had mild buccal crowding but no obvious reasoning for the differences could be observed. These differences were considered clinically relevant.

Interincisal width of the upper central incisor measured on the incisor that was opposite to the clefting defect demonstrated a significant outlier for subject 21. The measurements recorded for this subject were 6.61mm for plaster and 8.56mm for the Rhino software. This lead to a difference of 1.95mm. This would be considered to be significantly significant over such a short span. This subject had a significant class III incisor malocclusion with very rotated incisors. This may have made the contact points harder to identify, as the two central incisors were not adjacent to one another. This could potentially affect landmark identification and potentially account for the differences in the measurements that were obtained.

6.3 Hypothesis 3

'The time taken to produce MHB scores using the Rhino plug-in is no different to using existing methods with digital and plaster models.'

The time taken to record the MHB scores for each medium provided a basis for further research. As this was not the main focus of this project, time measurements were recorded only once for each measurement by the chief investigator for the total time to complete the MHB scores. The results show similar lengths of time to complete scoring for plaster and conventional digital model scoring. However, there is a dramatic increase in time needed to record the Rhino plug-in scores with approximately four times the time needed. Each time the script was run it took 3-5 minutes to complete the scoring and this varied between subjects depending on the teeth present. This is not a complete evaluation of the efficiency of scoring for the three models as does not take into account aspects such as unpacking or packing up stored models before and after scoring. The Rhino plug-in is at an early, relatively unrefined stage of its development, with multiple steps to complete the process for scoring models, and computer speed being a major factor in the efficiency of scoring.

A comprehensive evaluation of time efficiency of the algorithm could be completed once further development has taken place or an App developed for MHB assessment (Section: *6.11.3 App development*). This would provide a true reflection of the time efficiency for digital versus plaster models for scoring dental arch relationships. Differences with operator experience using the different mediums must be taken into account and the Rhino plug-in having not been previously used by the examiners. Investigators in this project have great experience with handling and manipulating plaster models for MHB assessment. Designed for CAD/CAM, the Rhino software is sophisticated but requires a degree of expertise and familiarity to use efficiently.

Time taken to record occlusal measurements has been investigated (Gracco et al., 2007). In this study an external investigator used a chronometer to determine the time taken to record a series of occlusal measurements for plaster and digital models. The digital measurements taken using a software measurement tool were found to take on average 6.525 minutes less, almost half the time taken than with plaster models and a Boley guage. This was significant ($p<0.0001$), however the experience of the operators with using the software was not commented on. This contradicts the results found in this study where both conventional digital MHB assessment and Rhino plug-in MHB assessment were slower than plaster measurements. However, the study is not directly comparable when the different methods of measurement made in the two studies is accounted for; linear measurements in one and the degree of crossbite discrepancy for MHB assessment in the other.

In a small study of 22 dental models, a comparison of time taken to measure and calculate the Bolton tooth size discrepancy was investigated for digital and plaster models (Tomassetti et al., 2001). Overall, all three software tools used to perform the task were quicker than measuring plaster models with vernier calipers. However, clinically significant differences of >1.5mm were found between measurements for all the digital methods used. It should be noted this study was conducted during the early stages of software development for orthodontic analysis, and results may be questionable against current technology.

In a more recent study, the time taken to record mesio-distal tooth widths from different perspectives on digital models was found to have significant differences (Horton et al., 2010). When viewing the digital model from the occlusal aspect the time to record occlusal measurements was much faster than measurements made by rotating the model.

It would be anticipated that the efficiency of scoring digital models and in particular the Rhino plug-in, will increase with further development and refinement to make the process quicker and more user friendly. It would also be expected to increase in efficiency with greater user experience.

6.4 Landmark identification and error study

6.4.1 Landmarks

Landmarks are used to represent anatomical structures. Digital landmarks used for this study were agreed and standardised by the investigators. Similar landmarks have been used in other studies to predict customised archforms for a selection of pre-treated malocclusions using polynomial curves (Adaškevičius and Vasiliauskas, 2009). Using 3D digital models, the x and y co-ordinates were used to represent archform. Twelve landmarks in total were identified for the mid-incisal points, canine cusp tips, buccal cusps of the premolars, and in contrast to this study, the distobuccal cusps of the first molars. The investigators used the most occlusal aspect of the mid buccal groove for the first and second molars. This prevented distortion of the buccolingual position of the molars when the teeth were significantly rotated. In addition, only one reference point was able to generate a precise horizontal distance for maxillary molars. It was agreed that the horizontal calculations were unlikely to be clinically affected by using this landmark instead of cusp tips.

Landmarks using occlusal cusps have also been used in a recent study for comparing maxillary and mandibular archforms using Generalised Procrustes Analysis (Papagiannis and Halazonetis, 2015). Twenty-two landmarks for the maxillary and 24 for the mandibular arch facilitated superimposition of the two archforms. These were computed in three-dimensions. A greater number of landmarks were required for the identification of posterior teeth to give an indication as to the inclination of the teeth. This information was not required in the present study; therefore only one landmark was identified for each posterior tooth.

The FA point, the midpoint of the facial axis of the clinical crown, has also been used to determine archform (Ronay et al., 2008, Bayome et al., 2011). This reflects orthodontic bracket position more accurately than cusp tips and incisal edges. This is particularly useful when determining archform for pre-adjusted and customised archwires. As this was not the aim of this project, it was felt the FA points would be inappropriate for the assessment of dental arch relationships. However, the algorithm could be adapted for use with such landmarks for the fabrication of customised archwires. This would have the potential of being inherently more stable if the transverse, antero-posterior and vertical planes were considered.

6.4.2 Landmark precision

Studies have investigated the precision of landmark identification for digital models in patients with clefting deformities (Brief et al., 2006). In a sample of 40 digital models from 20 patients with UCLP aged between 3 and 8 months, four experienced observers repeatedly identified 9 non-odontoid digital landmarks. Intra-observer error of landmark placement ranged from 0.61mm to 1.99mm. The landmark identification error was found to vary between the x, y and z axis for different landmarks. The study concluded that different observers could identify landmarks for the same studies (Brief et al., 2006). It also highlighted the importance of wash-out periods between landmark identification rounds. Whilst this study used different anatomical landmarks, it is interesting to note small degree of error in landmark precision within and between observers for digital models in patients with UCLP.

6.4.3 Error study

The results presented in this thesis show excellent intra-observer reliability of 0.933 using Cronbach's alpha. Unfortunately, there are no directly comparable studies, to which digital landmark identification for x, y and z variables can be compared to, when assessing anatomical landmarks on teeth in patients with clefting deformities. Therefore, this study could be considered a preliminary investigation for future research in this field. Inter-observer reliability was not measured in this study as it was not the main focus of this project and landmark identification was performed to demonstrate the error of the method by the chief investigator.

6.5 Standardisation

6.5.1 Viewing perspective

Standardisation during the digitisation of the digital models for landmark identification was achieved by tilting the occlusal plane on screen slightly away from the user before commencing assessment. This provided a good view of the occlusal and incisal surfaces. The software platform had a useful integrated reference plane that was highlighted when tilting the model. This enabled each examiner to tilt the model with reference to it, ensuring the landmarks were identified from similar occlusal plane views. This was deemed important by the investigators as it has been shown that the accuracy of measurements can be altered by different perspectives of digital models (Horton et al., 2010).

6.5.2 Magnification

Magnification of the digital model has been shown to affect linear measurements (Mullen et al., 2007). Mullen et al found that using a scanning device to create an OrthoAnalyzer™ digital model, produced on average 0.067mm of magnification from the plaster to digital image. Using machined ball bearings on digital models they also found that high magnification of digital models was linked with small improvements in accuracy on average 0.013mm. Therefore, to limit the variation in digital model size on screen between examiners, it was decided not to alter the size of the digital model after it had loaded into the Rhino software. A large monitor screen was used for the Rhino software so each examiner would have a sufficient magnification of the digital model for precise landmark identification.

6.5.3 Software requirements

Two different software tools were used to assess MHB scores for digital models. Unfortunately, these were not be identical. For conventional scoring of digital models with the MHB scoring system, OrthoAnalyzer™ Software (3Shape A/S, Copenhagen, Denmark) was used. The OrthoAnalyzer™ software was marketed for concurrent use with the R700 optical benchtop scanner used to create the digital models, therefore it simulated the technique of conventional assessment of dental arch relationships on digital models adequately. OrthoAnalyzer™ was not suitable for the design and construction of the automated software tool, as it was not a software platform that could be used to add functions and run scripts. Therefore, a requirement for a CAD software platform was needed. This created slight differences for viewing and manipulating the models between the two mediums.

Differences between OrthAnalyzer™ and Rhino included the on screen colour of the digital models. OrthoAnalyzer™ models were displayed in a light shade of brown, whilst Rhino displayed in grey. In addition, on screen manipulation of the digital models using the cursor was slightly different. The investigators could not have avoided these subtle differences, but it was felt they were unlikely to influence the results. Whilst there is an abundance of literature highlighting comparisons between digital models and the 'gold standard' plaster models (Fleming et al., 2011), there is none at the time of writing regarding direct comparisons between different software mediums.

6.6 Study population

6.6.1 Cleft type

The study population was taken from a similar study investigating the reliability of digital study models for scoring surgical outcomes in cleft care (Chalmers, 2015). Therefore the subjects for this study were pre-determined as a cohort of patients aged between 9-21 years and with UCLP. Although UCLP is the largest type of oral cleft, and patients within this defined age range are those likely to be undergoing active multidisciplinary treatment, ideally this algorithm would need to be tested on a larger sample with differing cleft types, and greater age ranges. The MHB scoring system has previously been shown to have good reliability for bilateral cleft lip and palates (Tothill and Mossey, 2007). However, the reliability of the MHB index on digital models for patients with BCLP has not been investigated yet. Younger cohorts of subjects with ages of 5 and 10 years have been investigated in individuals with UCLP using the MHB scales and have shown to have good intra and inter examiner agreement (Dobbyn et al., 2012).

6.6.2 Dental development

One limiting factor with the Rhino-plug in is the requirement of a dentate arch for archform construction using cubic splines and subsequent occlusal assessment. This precludes use of the current software tool for patients prior to the eruption of the primary dentition. Despite this, it would be possible to make adjustments to the existing algorithm to use anatomical markers on the alveolus, as has previously been explored for patients aged from birth to 8 months on digital models (Brief et al., 2006). This would almost certainly require an adjustment of existing scoring conventions and validation.

6.6.3 Sample size

The sample size was pre-determined in advance of subject recruitment for the study by Chalmers et al (2015), therefore no prospective sample size calculation was done for MHB scores on digital models. Instead the sample size calculation had been estimated for GOSLON categories as the sample was obtained from a previous study (Section:*4.10.3 study population*). However, observation of the confidence intervals for the Bland-Altman plots for the plaster and OrthoAnalyzer™ models showed that just over a mean difference of 4 points on the MHB scale, contained 95% of the data (Figure 20). As these mediums were regarded as the gold standard, a retrospective sample size calculation was undertaken to detect a clinical difference of 4 on the MHB scoring scale. MHB total scores from all three examiners were gathered to produce a standard deviation of 9.2. A power of 80% with a p value of 0.05 found a sample size of 40 would be required. As this study had 53 subjects, it was sufficiently powered for true inferences to be drawn about the methods used.

6.7 Occlusal indices

6.7.1 The GOSLON Yardstick

Most studies investigating dental arch relationship outcomes for patients with CL/P use GOSLON as an assessment tool (Jones et al., 2014). This index was originally validated for use on a cohort of 55 selected patients with UCLP (Mars et al., 1987). No sample size or randomisation was performed. Intra and inter-observer reliability was tested using Wilcoxon's test and found to be high ($r \leq 0.92$). In the discussion section, Mars et al (1987) concluded that finer distinction between the categories would be merited if comparing two groups spanning consecutive categories (i.e. groups 1 and 2). Furthermore, they suggested that this could be implemented with the aid of the Huddart and Bodenham scoring system proposed in 1972.

After the GOSLON yardstick was adapted and validated for the early mixed dentition to become the 5 Year's Index (Atack et al., 1997), the two indices were investigated for predictive long term outcomes in UCLP. In a study involving 94 patients with UCLP, longitudinal records were selected at 5 and 10 years and scored using the two methods at 5 years, and the GOSLON index at 10 years (Mars et al., 2006). This highlighted the lack of consistency of the scoring method over time, with the agreement of GOSLON scores for 5 and 10 year old models showing only a moderate strength in agreement at 0.539 using the kappa statistic. The 5-year index scored at 5 years was compared with the GOSLON index at 10 years. Poor agreement (kappa value 0.043) was found. The authors of the study concluded that the 5-year old index was not a reliable indicator for longitudinal outcomes at this age (Mars et al., 2006). Alterations to the GOSLON Yardstick were suggested instead. These conclusions were drawn despite finding that longitudinal agreement using the GOSLON Yardstick alone was only moderate.

The simplicity of the GOSLON yardstick and its rapid assessment in application has been suggested to be its greatest strength (Mars et al., 2006), in addition to its ability to assess dental arch relations in three planes of space. However, its very nature as a subjective tool can lead to categorisation ambiguity (Mossey et al., 2003). The GOSLON system lacks sensitivity as highlighted by a large international study, 'in order to detect a difference of 0.5 at 5 per cent probability and with 80 per cent power, an annual case load of some 60 patients over a period of 8.5 years is required'(Shaw et al., 1992). Many clinicians in the UK do not pertain to have such a significant caseload, despite the re-organisation of cleft services following the CSAG report. Further to this, the GOSLON Yardstick relies on regular examiner calibration, which can be costly and time consuming. Therefore, other indices with greater sensitivity such as the MHB scoring index would be best suited for estimating surgical outcomes. This conclusion was reinforced in a recent Canadian study which compared various indicies used in cleft outcome measures (Altalibi et al., 2013).

6.7.2 Huddart and Bodenham scoring system

The development of the Huddart and Bodenham scoring system as a more reliable scoring system for clefting defects began with a preliminary investigation (Mossey et al., 2003). Since this time it has been successfully evaluated (Gray and Mossey, 2005), modified further, and calibrated to scoring categories for the GOSLON Yardstick (Dobbyn et al., 2012). It has also shown to be reliable for the assessment of dental arch relationships on patients with

BCLP (Tothill and Mossey, 2007) and to be more reliable than the EUROCRAN Yardstick (Patel, 2011). In a systematic review of the indices used to assess malocclusions in individuals with CL/P, the MHB index was viewed to be superior in terms of the WHO criteria for an ideal index, despite the GOSLON Yardstick being the most commonly used (Altalibi et al., 2013). Recommendations were made that this index should be used to standardise outcomes in cleft care in order to optimise cleft outcomes and facilitate multicentre research investigations.

Investigators of the MHB index (Gray and Mossey, 2005) have previously suggested that this index would lend itself to application with digital models. This has now been achieved, and results have shown excellent agreement when compared to conventional plaster models (Chalmers, 2015). It has also been postulated that development of a computer program to increase the efficiency of MHB scoring would be beneficial (Gray and Mossey, 2005). The results presented in this thesis are the first step into the development of such an automated system to assimilate MHB scores and increase efficiency. It has also been influential in highlighting the degree of accuracy that can be achieved with such a system.

6.8 Digital study models

Digital models are now an accepted method of record storage over traditional plaster models. They are an acceptable medium for assessing both linear and angular measurements (Fleming et al., 2011). Orthodontic indices have also shown to be reliable, such as the IOTN (Sharma et al., 2013). In a systematic review the absolute mean difference between measurements made on plaster and digital models for a number of parameters is small and likely to be clinically insignificant. Recommendations have been made for digital model use over more traditional plaster models (Fleming et al., 2011). However, caution should be observed with the quality of some of the studies that were included. Digital models for CL/P outcomes have also been verified for GOSLON and MHB scoring (Chalmers, 2015). No clinically significant differences between plaster, OrthoAnalyzer™ digital models produced by scanning plaster models, or direct digital models produced from intra-oral scanning of the dentition were found. Furthermore, a piloted questionnaire completed by both the subjects and their parents following intraoral scanning and an alginate impression, showed a highly significant preference (p=0.00018) for the intraoral 3D scanning device (Chalmers, 2015). It is likely that intra-oral scanning of the dentition to produce digital models will become the preferred method in the future.

6.9 Archform algorithms

6.9.1 Cubic splines

The work presented in this thesis uses cubic splines as an assessment of dental archform. Cubic splines offer the advantage that they accurately represent shapes in three planes of space. It was first described for the computerised 2D analysis of dental archform by Begole (Begole, 1980, Begole, 1979). This project has taken the cubic spline into the third dimension, advancing techniques as technology becomes more sophisticated. Other methods that have been described for archform assessment are the ellipse, catenary curve, parabola, hyperbola, conic sections, polynomial functions of varying degree, EDMA, GPPA and beta functions to name just a few (Papagiannis and Halazonetis, 2015). The majority of these methods describing the ideal archform, display or impose arch symmetry, which cubic splines do not. This is of importance in severe malocclusions such as clefts, where a greater tendency for asymmetry exists (Hechter, 1978).

6.9.2 Generalised Procrustes Analysis (GPA)

In this study it was not the intention to describe or prescribe the ideal dental arch relationship, merely to describe the existing maxillary and mandibular archform in relation to each other. Studies investigating and comparing dental archform of maxillary and mandibular arches have more recently used the Generalised Procrustes Analysis (GPA) (Nam et al., 2012, Papagiannis and Halazonetis, 2015, Moss, 2006), as a technique to superimpose the two archforms using an optimising technique to rotate, translate and scale the dental arches. This is a useful technique, however, the cubic spline was felt to be superior for use in this project as it was only needed in a single arch. In this case the mandibular arch, to which the maxillary identified landmarks could be assessed. In addition, a complete dental arch was not always present due to the inherent nature of the orofacial cleft abnormality and range of ages examined. This would have made superimposition of the dental arches difficult using the GPA method. Exceptions and adaptations for missing teeth were most frequently needed, and this could easily be applied using the cubic spline.

6.9.3 Archform in Orthodontics

Archform analysis and customisation is frequently required in orthodontics for describing dental arch relationships, and prescribing treatment mechanics. One area where this is most frequently encountered is in the use of orthodontic archwires. Archwires that are commercially available come in a range of preformed sizes. This increases efficiency by reducing wire bending and enhances stock control efficiency. Nevertheless, they still require adaptation if the existing archform is to be maintained, as many commercial archforms are not ideal for untreated malocclusions (Felton et al., 1987).

The Rhino plug-in assessment of the maxillary and mandibular archform has the potential to be adapted for use in the commercial manufacture and customisation of archwires in inherently asymmetric archforms, where maintenance of the asymmetry is desirable. Such would be the case as in patients with clefting defects, where positioning of teeth symmetrically maybe out with the alveolus within or adjacent to a cleft defect. This CAD-CAM approach on digital models in such malocclusions could potentially lead to greater stability of the arches due to reduced alteration of the existing archform (Little, 1990).

6.10 Algorithms in healthcare

6.10.1 Medicine

Algorithms are the cornerstone of modern healthcare systems for a variety of clinical and non-clinical applications. Computer aided diagnosis and electronic health data has expanded to equip individuals and organisations with new technologies for rapid disease identification and prevention strategies. Automated surveillance systems for healthcare associated infections (van Mourik et al., 2013), decision making for treatment diagnosis and planning (Shah et al., 2002, Lin et al., 2014) and the development of phenotype algorithms for clinical and translational research (Mo et al., 2015) have all been described. For example, electronic medical health records (EMRs) have been examined using phenotype algorithms to search for patients with primary hypothyroidism and match them to patients without hypothyroidism, enabling genetic analysis of DNA biobanks linked to EMRs, to identify genetic risk factors associated with the disease (Denny et al., 2011).

6.10.2 Dentistry

The dental sector has had equal success in technological advancement with its medical counterparts. Emerging algorithmic tools are available as an aid in diagnosis and treatment such as the UK based program OPAL (www.opalimage.co.uk) for cephalometric tracings, predictive surgery outcomes and photo morphing. Dolphin imaging (www.dolphinimaging.com) orthodontic software, has also been designed for clinicians and laboratories to simulate treatment outcomes, evaluate 3D measurements and 2D archform analysis with digital images. Furthermore, OrthAnalyzer™ (3Shape, Denmark) a digital image system that facilitates 2D archform construction with splines and PAR analysis using customised user prompts, is one of many available commercially. A fully automated system has not yet been proposed for orthodontic indices such as PAR, IOTN, ICON, or any of the cleft care indices, such as GOSLON, despite their frequent use in the UK. This research could be instrumental to researchers developing the concepts for automated approaches to such indices.

Algorithms are also used to simulate treatment outcomes for customised 3D appliance construction. For example Clincheck®, a software program tailored for clinicians aligning teeth with clear aligners made by Invisalign® (www.invisalign.co.uk), is underpinned by algorithms that simulate an ideal occlusion on digital models. This in turn facilitates a series of custom-made appliances to be made. 3D appliance construction is advancing with uses for indirect bonding tray fabrication, palatal and lingual custom appliance design and construction, and clear aligner technology (Martin et al., 2015). Algorithms have reduced the need to manually customise appliances chair-side, by enabling much of the customisation to be done digitally.

Algorithms in healthcare, are often not made available by commercial companies for financial gain. Individuals in dentistry and medicine wishing to develop new algorithms for advancing healthcare are often restricted by expertise and methods. It is hoped that making the algorithm presented in this thesis available, individuals will find guidance in this methodology for future healthcare application.

6.11 Critique of the study

6.11.1 Strengths

- This study shows that technological advancement can improve our accuracy of outcome measures in cleft care.
- It is a novel method that has not been previously described or tested.
- The use of three raters to examine inter-observer reliability in validation of the Rhino plug-in facilitated greater weighting to the statistical analysis.
- Strict calibration guidelines were dictated for each observer prior to using the Rhino plug-in.

- The study makes available the detailed mathematical and computational approach to clinicians wishing to develop such an automated system for their own clinical environment.
- It provides a stepping-stone to further technological advancement such as development of an App.
- There is demonstration that successful collaboration with other specialties, such as computer science and mathematics, can develop transferable skills and methodologies that could be applied in other fields, whilst creating new opportunities for further research.

6.11.2 Weaknesses

- This study has validated an algorithm for one cleft subphenotype. Further validation of the software would be required to extend its use to other cleft types such as bilateral cleft lip and cleft palate only deformities.
- Observers in this study to examine intra-rater and inter-observer reliability were all from one hospital department with clinical interests in Orthodontics. Extending the validation of the software using non-clinical observers would confirm whether the use of the Rhino plug-in could be used by other health professionals. This would be beneficial for busy cleft units where clinicians may not have the time to complete the scoring.

- The MHB assessment currently excludes an assessment of the vertical component of surgical outcome. Although this could easily be incorporated to the Rhino-plug-in this was not validated. This is one area that despite its more objective system, where the MHB index is inferior to the GOSLON Yardstick and 5 year index.
- The software tool that was developed is still in a relatively early stage of development and not robust enough for routine clinical use. There are many stages to the operation of the scoring process. Each must be completed in sequence, otherwise the script will terminate. A more robust system with fewer steps could be developed with adaptation. It would also be beneficial for the tool to be developed into a single software package rather than as a 'plug-in' for a software platform. Rhino has been an appropriate platform package for the development but a more user-friendly software or app would be required for routine scoring.
- Using two different software tools to evaluate MHB scores for the automated and conventional method of assessment may have led to small differences between the data sets. It has not been confirmed whether this would have been clinically significant.
- Unfortunately a prospective sample size specifically for MHB scores was not calculated, as the number of subjects within the study had been determined prior to this research. A retrospective sample size was calculated to detect a clinical difference of 4 between MHB scores,

equating to less than 1 GOSLON Yardstick category, which indicated sufficient power for this study. However, if this study were to be repeated, a larger sample with a smaller clinical difference in MHB scores would show the accuracy of this new automated tool with greater confidence.

6.12 The future

The impact of digital technology has been profound across many sectors including science, engineering, mathematics, healthcare and more recently in the construction industry (www.3dprinthousecanal.com). CAD/CAM was first made available commercially for use in a dental application approximately 30 years ago, (Mörmann et al., 1985) a decade after the concept of dental intra-oral scanning was introduced (Duret, 1973). Since this time, many more commercially available devices and software packages for all branches of dentistry, not least orthodontics, have been made available.

6.12.1 Adaptation of the existing software tool

This software development described in this thesis has automated the method proposed by Mossey in 2003 (Mossey et al., 2003). It uses the horizontal component of dental arch relationships in determining the MHB score for each corresponding tooth pair. One limitation of this method is that it ignores the vertical component of a malocclusion, which can be unfavourable especially in patients with congenital birth defects. The GOSLON Yardstick (Mars et al., 1987) is currently one of the few indices to include the vertical component, however the subjective nature of this index precludes any clinical meaningfulness to this dimension. Only in unfavourable cases will the vertical dimension affect the categorising of a malocclusion using the GOSLON Yardstick.

Overcoming vertical limitations, the vertical dimension could be incorporated into the MHB index by utilising the vertical distances automatically produced in this software tool. In a similar fashion to the allocation of scores for the horizontal dimension, the vertical dimension could be allocated a score. This could either be incorporated into the overall MHB score or used as an adjunct to create a two part MHB score. Further research would be needed to validate this addition to the scoring system.

Adaptations for different cleft types and ages, would be beneficial for longitudinal studies and comparisons. This has previously found to be a limitation of common surgical outcome score indices (Mars et al., 2006). Alterations in landmark definition and distance constraints could be made to suit the malocclusion. Automatic recognition by the software of the patient's age from the patient identifier could also be incorporated to adapt the algorithm accordingly.

6.12.2 User-friendly adaptation

The next stage in development of the software tool for clinical use would be to formally transfer the Rhino script into a more user friendly application or software. At present the software tool is bulky and liable to terminate if tasks are not completed in sequential order. Automating certain steps could make improvements in efficiency. For example, automation of the process to convert the digital model from a triangulated mesh to a rendered, more recognisable image, could be achieved. This would permit robust efficiency studies comparing the time taken to score plaster models and using an automated MHB software tool.

The software tool could be significantly streamlined by employing automatic recognition software for automatic landmark identification. This technology has been employed successfully in automatic face recognition from both 3D static images and 3D videos (Hayat et al., 2012, Best-Rowden and Jain, 2015). Such technology is able to recognise landmarks and features automatically without being affected by the viewing perspective (Asthana et al., 2011). Similar technology could be employed for the recognition of cusp tips, thereby limiting examiner subjectivity entirely.

6.12.3 App development

Software is an integral part of dentistry and orthodontics whether this is through appointment booking software, cephalometric analysis software, PAR/IOTN assessment software, or with the largest rise in software downloads, mobile apps. Mobile apps have stormed the technology industry with apps available in most sectors. It is suggested that the increase in app downloads is a direct result of the increase in sales of smartphones over recent years (Voas et al., 2012). Garnter Inc, one of the world's largest IT research analysis companies predicts that during 2017 almost 270 billion apps will be downloaded, with over 90% of the apps downloaded free of charge. An article looking specifically at orthodontic apps on smartphones concluded that all of the apps found up to December 2013 were for either Android, Apple, iPad or iPhone operating systems (Baheti and Toshniwal, 2014). Seventy apps were orthodontically relevant, although caution should be taken when interpreting the usefulness of such apps as un-regulation can lead to limited and inaccurate information for patients.

This project could be regarded as a pilot study for the development of an App for the assessment of surgical outcomes in CL/P patients. There is no App currently available for download for the assessment of surgical outcomes in CL/P. It is envisaged that an App could be developed using the existing software code within this project. Identification of digital landmarks could be achieved with touchscreen technology or with automatic landmark recognition. Links to online registries such as EUROCAT, CCS or CRANE could be provided for streamlining the entry of database outcomes. Personal data confidentially would need to be considered a priority for App development if digital models of patients are to be used.

6.12.4 Global application

A recent report from the Aalborg University of Denmark suggests that whilst the software industry is booming there is a shift in the global innovation map (Lema et al., 2012). India has now become one of the world's largest software producers as a result of a shift in financial power, away from developed countries. This has occurred as a result of the global financial crisis. It is suggested that low wages for highly educated individuals, the return of migrant engineers, scientists and, mangers, the insertion of local firms in global value chains, and 'local enterprises circumventing intellectual property rights of foreign firms' are some of the reasons for this global phenomenon. This could be beneficial for cleft care with the potential for software assessing surgical outcomes to be directly implemented into these communities where high CL/P rates exist with low outcome reporting. Therefore this project and further concurrent research could be influential in establishing advanced methods in the developing world for the assessment of dental arch relationships for patients with CL/P.

6.13 Impact of this study

6.13.1 Outcome indices

Knowledge of both qualitative and quantitative outcomes, in an effort to understand clinical performance, patient reported outcomes, burden of care and the healthcare impact on quality of life in orofacial clefting, has expanded. There are many outcome measures in cleft care owing to the vast number of specialties involved (Jones et al., 2014). It cannot be expected that one index fits all, if it is to be specific in what it measures. Outcome measures investigating dental arch relationships are essential if we are to understand the effects of our treatment and interventions, in an effort to establish optimal care.

Research into methods determining acceptable and unacceptable care, have been considered to be high priority (Mossey et al., 2011). Therefore, the significance of an accurate index of clinical performance presented here, with the potential to replace less specific and subjective methods of assessment such as the GOSLON Yardstick and 5-year old index, should not be underestimated. The MHB scoring system has already been found to be a more sensitive method for detecting subtle changes in dental arch relationships than previous indices (Dobbyn et al., 2012). Therefore, an automated approach that is more consistent than the previous MHB scoring methods, has the potential to optimise techniques and protocols.

Valid and reliable surgical outcome measures and indices of facial growth are necessary to understand the effects of intervention in accountability, health-care design and improvements in quality (Sitzman et al., 2014). Outcome measures can be investigated from different perspectives such as the patient, the family, the service provider the financier (Sitzman et al., 2014). However, there is distinct overlap between them. Therefore, it must be recognised that any intervention should be investigated from each of the four domains. The MHB Rhino-plug is largely an assessment from the clinical perspective. Therefore, it could be coupled with outcome measures from the patient, family, and financier to provide a fully holistic measure of any intervention.

As a numerical scoring system with a high degree of accuracy, scores could be weighted to integrate with other outcome measures, to provide a truly meaningful assessment of outcome in cleft care. This has been achieved in other orthodontic indices such as the Index of orthodontic complexity, outcome and need (Daniels and Richmond, 2000), which includes the aesthetic index of treatment need as viewed by the patient.

6.13.2 Quality of Life/ burden of care

There are three groups of individuals affected by OFC that have been recognised for targeted research into the impact of this abnormality. These are individuals with un-operated clefts, repaired clefts and no residual deformity, and repaired clefts with a residual deformity (Mossey et al., 2011). The differentiating factor between these groups is the surgical intervention. Understanding this in terms of the psycho-social impact such as school attendance, days spent in hospitals, pain, family and friend relationships, will give an indication to the true burden of care that individual faces and how this can be minimised.

There has been much interest in the burden of cleft care, from excessive interventions, to affected children and their families. Pre-maxillary orthopaedics is one area that has spurned much debate over recent years. Consensus appears to be forming that there is little evidence to support the benefits of this intervention long term when weighed against the significant burden of care for individuals (Uzel and Alparslan, 2011). More well-controlled trials have been called for to address the lack of long-term high quality trials (Shaw, 2004a). This is important if we are to integrate evidence-based medicine into contemporary cleft practice.

6.13.3 Global database

A global report on health strategies highlighted epidemiological data in orofacial clefting has significant international variation owing to differing methods of ascertainment, making comparability of data challenging (Shaw, 2004a). Furthermore, many areas of the globe have little or no epidemiological data on clefting defects as birth surveillance systems are limited (Mossey and Modell, 2012). Valid, standardised outcome measures, such as the MHB index and Rhino-plug-in, has the potential to encourage counties to contribute data to global registries. As a universal scoring method, that does not require sophisticated calibration courses and anchor study models, it has advantages over existing methods for such purposes.

Adoption of a single yet reliable method of recording surgical outcomes by international collaborative centers will enhance comparative research studies and enable subtle differences in global techniques to be established. Numerical MHB data can easily be fed back into the WHO database for assimilation with the craniofacial anomalies project. Ultimately, as we understand the effects of surgical intervention and optimal techniques, the burden of care for individuals born with a cleft defect will be reduced.

CHAPTER SEVEN: CONCLUSIONS

The objective of this project was to design, calibrate and validate an automated software tool for the assessment of objective outcomes in individuals born with unilateral cleft lip and palate.

- The Rhino automated software plug-in tool produced MHB scores that were no different to manual methods of MHB scoring using plaster or digital models. The Rhino plug-in was a more consistent and reliable method of scoring.

- Intra- and inter-observer reliability for MHB scoring using the automated Rhino plug-in software and manual methods were excellent. The Rhino plug-in displayed the highest agreement for repeated measurements.

- The Rhino plug-in software tool produced similar measurements to manual measurements from plaster models. The only significant difference was noted to be between inter-molar and overbite measurements where the mean differences were not considered to be important clinically. Measurements made using the Rhino software were reliable.

CHAPTER EIGHT: REFERENCES

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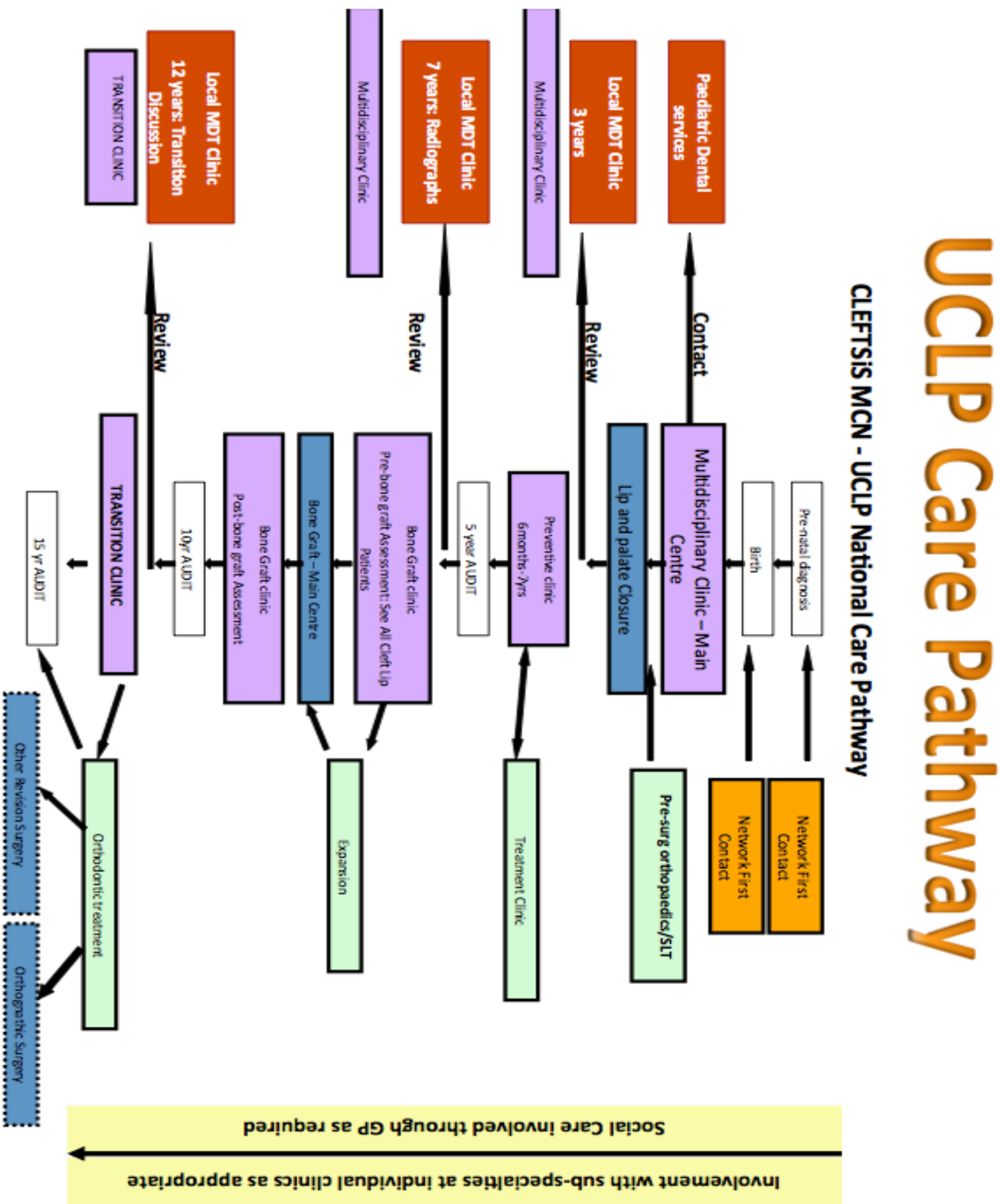
CHAPTER NINE: APPENDICES

Appendix I

CCS cleft pathway for patients with UCLP.



Appendix II.

Mathematical modeling for construction of the mandibular cubic spline.

Given n mandibular cusps, Pixi,yi,zi, i=1,⋯,n, a cubic spline St of n-1 piecewise polynomials Si(t), i=1,2,⋯,n-1, can be interpolated to the maxillary cusps. The spline can be expressed as:

St=S1t=al+b1t+c1t2+d1t3, S1t is between P1 and P2 S2t=a2+b2t+c2t2+d2t3, S2t is between P2 and P3 : : Sn-1t=an-1+bn-1t+cn-1t2+dn-1t3, Sn-1t is between Pn-1 and Pn.

There are 4(n-1) unknowns ai,bi,ci,di, i=1,2,⋯,n-1. In order to get the solution of all the unknowns, 4(n-1) equations are needed. Each cubic spline goes through two consecutive points, e.g. Sit goes through Pi and Pi+1. This condition gives 2(n-1) equations. The first and second derivatives of two cubic splines are continuous at the interior points. This condition gives 2(n-2) equations. Two more constraints are usually specified as boundary conditions at the endpoints. Usually “natural” endpoint conditions are applied as the vanishing of the second derivatives at both ends. All together 4(n-1) equations are constructed to build a system and give solution for the 4(n-1) unknowns of the expression of the cubic splines.

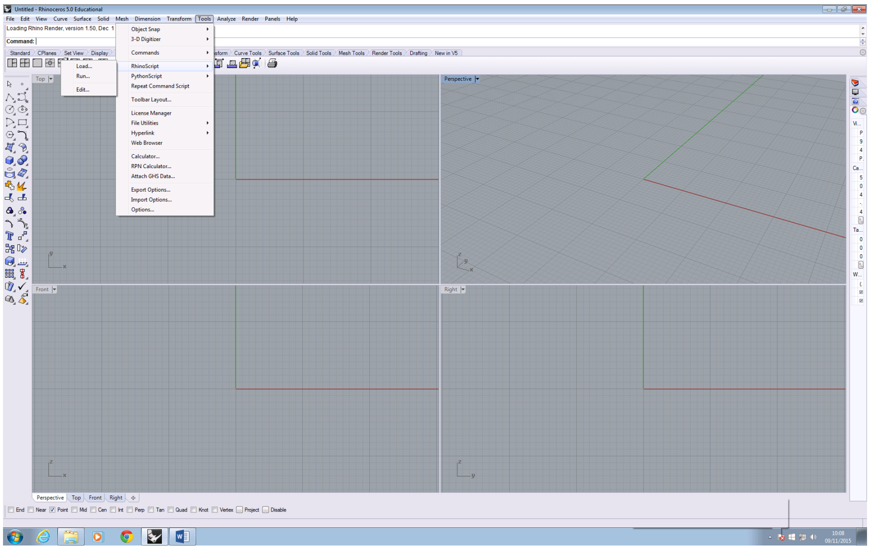
<u>Mathematical modeling for construction of the sign to represent the bucco-lingual relationship of the maxillary and mandibular teeth.</u>

Let tj be the tangent at Qj’ along the spline S. Let Vj be the vector from Qj’ to Qj, i.e. Vj=Qj-Qj’. If the dot product of n with the cross product Vjxtj is positive, i.e. n·Vjxtj>0, Qj is buccal to the spline then dhj is positive. Else if, n·Vjxtj<0, dhj is negative. If n·Vj>0, Qj is above of Qj’ and dv is positive. Else if n·Vj<0, Qj is under of Qj’ and dv is negative.

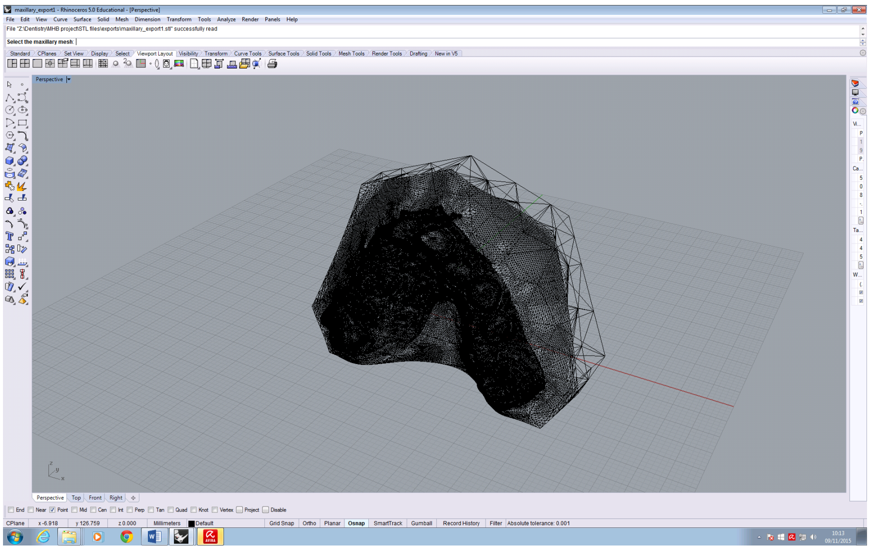
Appendix III.

Images displaying the operating steps using the Rhino pug-in for the calculation of MHB scores.

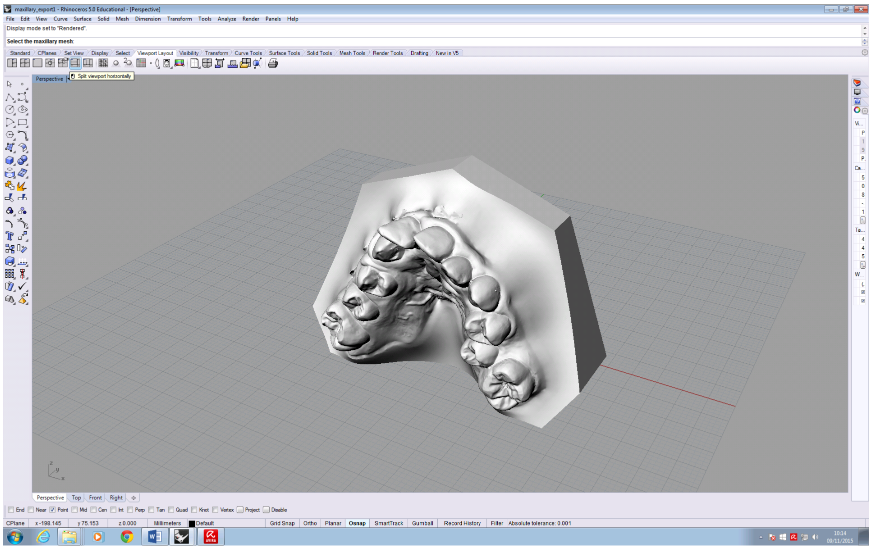
Step 1. Open Rhinoceros, version 5 and load script.



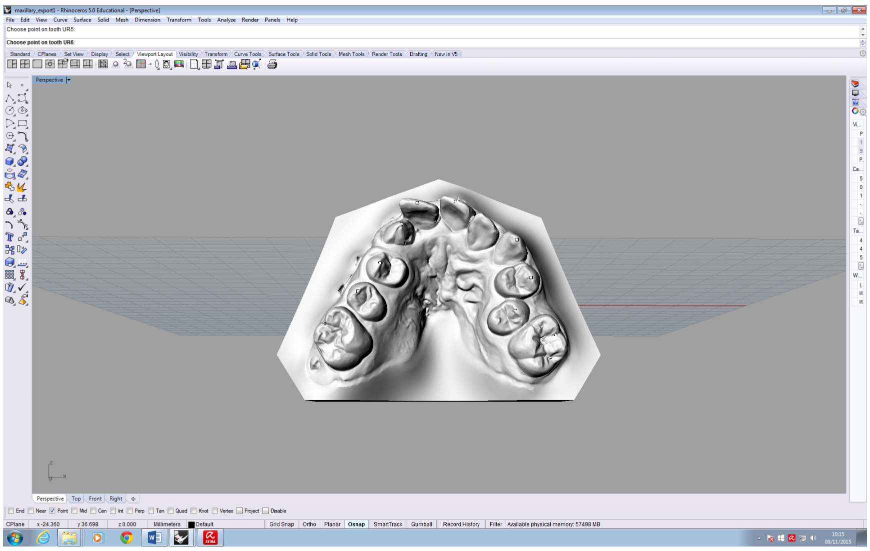
Step 2. Open the maxillary STL for the digital model to be examined



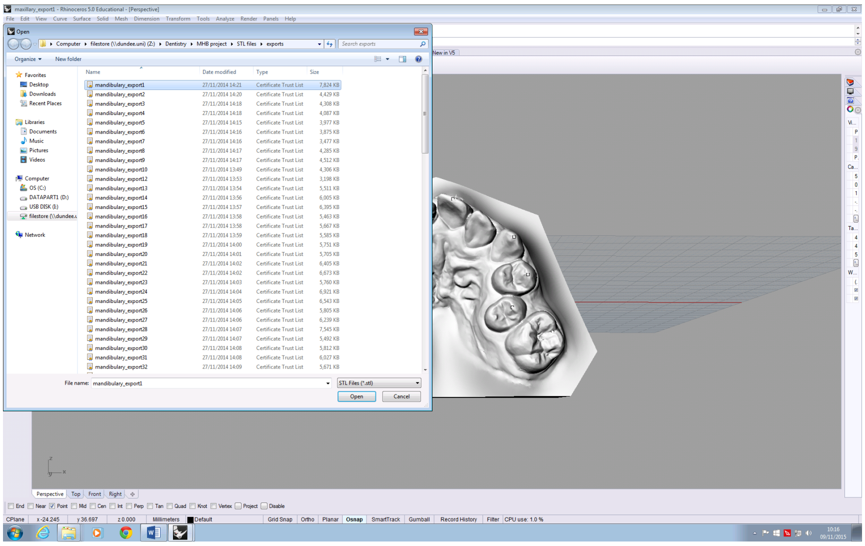
Step 3. Render the STL file



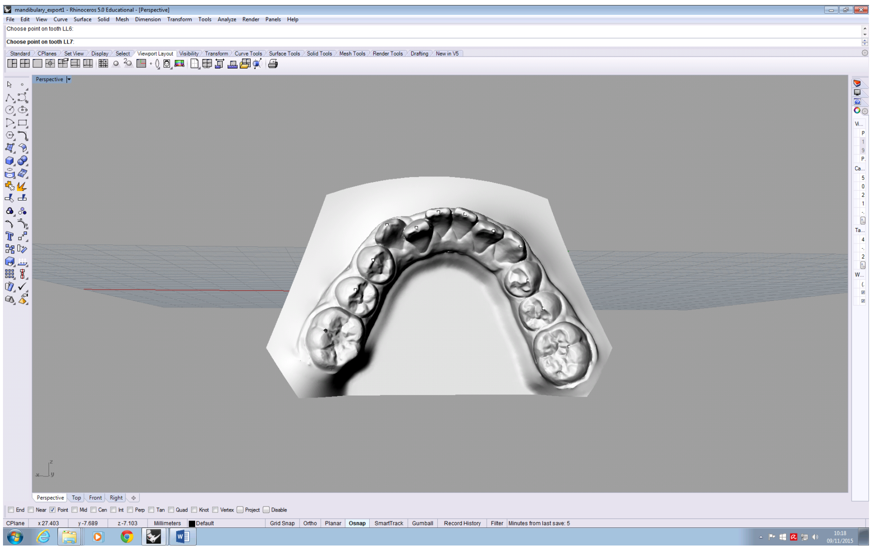
Step 4. Rotate image and choose maxillary cusp tips for scoring



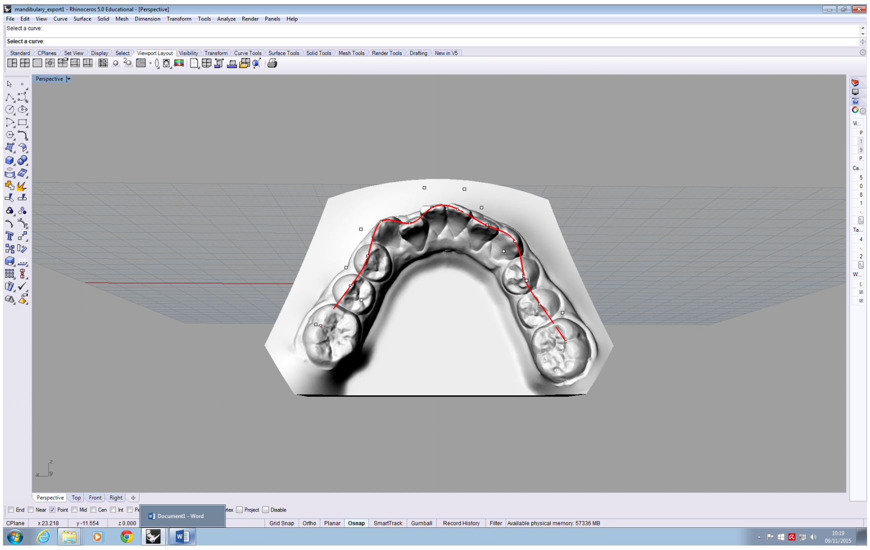
Step 5. Load the mandibular STL file, render the image and rotate for viewing



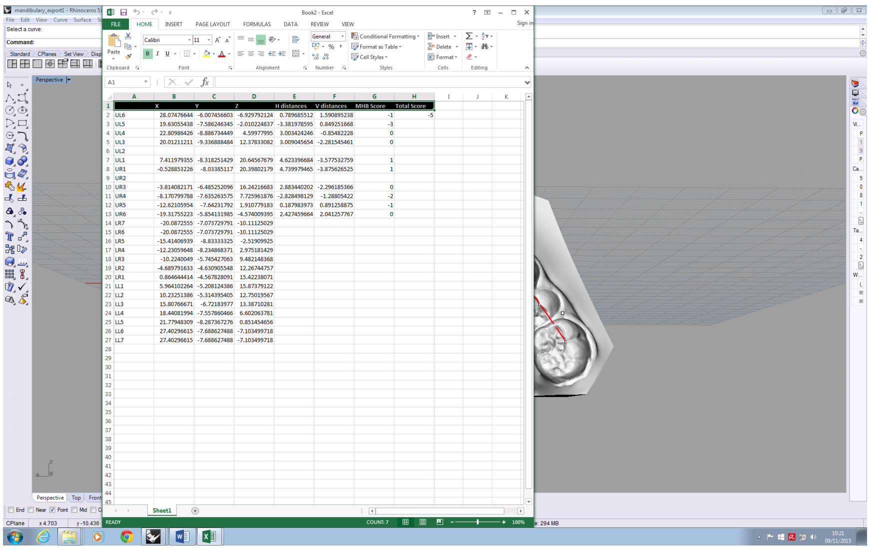
Step 6. Identify the landmarks for the mandibular dentition



Step 7. An automated cubic spline will be generated and the associated maxillary landmarks plotted



Step 8. The MHB scores will be automatically outputted into an Excel spreadsheet



Appendix IV.

Written instructions for calibration of the examiners for scoring MHB using the Rhino software tool.

Operating the script

- Start up computer on 7th floor DDH
- Log in to *Catherine* password ****** (case sensitive)
- Start Menu - Open Rhinoceros 5 (64-bit)
- Start Menu – Open *My computer*
- Click on Filestore (\\dundee.uni)(Z:)
  Enter password ****** (case sensitive)
- In Rhino go to *Tools* (top horizontal bar)
- Click on *Rhinoscript*
  Load
- Click on script in the box (Z:\CMDN\dent……etc)
  Load
  Automatic tab opens with STL files
- Chose the MAXILLARY model required for scoring
- Click Open
- Press Enter – a model mesh will appear – this may takes a few seconds
- The model on the top right with have a small tab in the corner labeled *perspective*– double click this tab and it will enlarge the mesh
- Click the small drop down arrow next to *perspective* label and choose *Rendered*
- Click the cursor on the maxillary model
- To rotate the model hold the right mouse button down & to enlarge use the scroll
- The software will prompt you (top horizontal bar) to click on the tooth required for scoring. Please stick to the order prompted otherwise you must start from the beginning!
- After last landmark has been clicked, a tab will automatically open.
    - Select corresponding MANDIBULAR model
    - Click open
- Press Enter
- Double click *perspective*
- Drop down box next to perspective and change to *Rendered*
- Click cursor on mandibular model
- Rotate model to view teeth

- Prompts will guide user to identify teeth
- Last tooth identified, a red spline will appear
- Click the red spline (anywhere)
- An excel spreadsheet will automatically open with results.
- Close spreadsheet once results have been noted
- Start from *Tools* in Rhino to load the next script, follow instructions and score next model

Landmark identification

- Most buccal point on the groove between the mesial and mid buccal cusps of the lower first molar, or any deciduous molar. This accommodates for any rotational discrepancies of the molars.
- Buccal cusp tips of the first and second premolars, where erupted.
- Cusp tip of the canines.
- Mid point of the incisal edges for all incisors.

Scoring considerations

- Maxillary 2's or 7's are not included in landmark identification
- All mandibular teeth, including 7's, are included for landmark identification
- If a tooth is missing click the tooth next to it twice at the same point and carry on
- If 7's are not present, double click the 6 twice
- If in the mixed dentition – same rules apply for manual MHB
- If a tooth is missing and the space is open then use the midpoint of the alveolar ridge where the tooth is likely to erupt or be positioned.

Appendix V.

Ethical approval confirmation by the West of Scotland Research Ethics Service for the study investigating MHB/ GOSLON scoring systems on plaster and digital models for patients with UCLP.

WoSRES
West of Scotland Research Ethics Service

NHS
Greater Glasgow and Clyde

West of Scotland REC 5
Ground Floor - Tennent Building
Western Infirmary
38 Church Street
Glasgow
G11 6NT

Miss Elinor Chalmers
Orthodontic Specialty Trainee
NHS Tayside
Dundee Dental Hospital & School
Park Place
DUNDEE
DD1 4HR

Date 08 January 2014

Direct line 0141 211 2102
E-mail WoSREC5@ggc.scot.nhs.uk

Dear Miss Chalmers

Study title:	**Intraoral three dimensional scanning for assessment of surgical outcome in patients with cleft lip and palate.**
REC reference:	**13/WS/0269**
Protocol number:	**2013DE05**
Amendment number:	**1**
Amendment date:	**28 November 2013**
IRAS project ID:	**117053**

Summary of amendment: *To extend the upper age of the inclusion criteria to 21 to allow eligible teenagers and young adults to be recruited to the study.*

The above amendment was reviewed by the Sub-Committee in correspondence.

Ethical opinion

The Sub-Committee had no ethical issues with the amendment and were happy to approve it.

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

Approved documents

The documents reviewed and approved at the meeting were:

Document	Version	Date
Notice of Substantial Amendment (non-CTIMPs)	1	28 November 2013
Participant Consent Form: Young Person	3.0	28 November 2013
Protocol	2.0	28 November 2013
Participant Information Sheet: Age 16-21	1.0	28 November 2013

Appendix VI.

Caldicott approval granted by NHS Greater Glasgow and Clyde for use of the STL digital files within the current project.

Acute Services Division

NHS
Greater Glasgow and Clyde

Department of Information Services
Administration Building
Western Infirmary
Dumbarton Road
Glasgow G11 6NT
Tel 0141 211 1790
Email Isobel.brown@ggc.scot.nhs.uk

Date 13th August 2014
Your Ref
Our Ref

Ms Catherine Martin
Orthodontic StR
Dundee Dental Hospital

Dear Ms Martin

Re: Re-use of data from intra-oral 3D scanning for assessment of surgical outcome in patients with cleft lip and palate project

I can confirm that Caldicott approval has previously been sought and given for the above project.

I have also approved, on behalf of the Caldicott Guardian, the re-use of the data collected from this research project for your own project, which I understand is looking at the development of an algorithm for calculating a singe Modified Huddart/Bodenham and GOSLON score to look at surgical outcomes in cleft lip and palate patients.

This approval has been given on the basis that no contact with patients is required and the project is linked to the previous study outlined above.

Yours sincerely

IBrown

Isobel Brown
Information Governance Manager

Delivering better health
www.nhsggc.org.uk

40389

Appendix VII

MHB score results for plaster models, OrthoAnalyzer™ models and Rhino plug-in, from each examiner.

MHB scores from examiner one -PLASTER

Examiner	Subject number	Sample	MHB RHS	MHB Incisors	MHB LHS	MHB total
1	1	1	-3	0	-5	-8
1	1	2	-5	0	-5	-10
1	2	1	-8	0	0	-8
1	2	2	-6	0	0	-6
1	3	1	-1	0	0	-1
1	3	2	-2	0	0	-2
1	5	1	-8	-6	-8	-22
1	5	2	-7	-5	-8	-20
1	6	1	-7	-2	-9	-18
1	6	2	-7	-1	-8	-16
1	7	1	5	2	-3	4
1	7	2	6	2	-4	4
1	8	1	-4	-4	-3	-11
1	8	2	-3	-4	-3	-10
1	9	1	-9	-4	-9	-22
1	9	2	-9	-6	-9	-24
1	10	1	-3	-4	-8	-15
1	10	2	-3	-4	-8	-15
1	12	1	-3	1	-5	-7
1	12	2	-1	0	-3	-4
1	13	1	0	2	-2	0
1	13	2	1	2	-2	1
1	14	1	-4	-5	-7	-16
1	14	2	-3	-5	-7	-15
1	15	1	-3	-5	-6	-14
1	15	2	-3	-5	-4	-12
1	16	1	-1	1	1	1
1	16	2	-1	2	1	2
1	17	1	0	-1	-2	-3
1	17	2	0	-1	-1	-2
1	18	1	-4	-4	-8	-16
1	18	2	-4	-4	-8	-16

1	19	1	1	2	1	4
1	19	2	1	2	0	3
1	20	1	0	2	0	2
1	20	2	0	2	0	2
1	21	1	-8	-6	-3	-17
1	21	2	-8	-6	-1	-15
1	22	1	-9	-6	-7	-22
1	22	2	-9	-6	-8	-23
1	23	1	0	0	0	0
1	23	2	0	0	-1	-1
1	24	1	-11	-6	-7	-24
1	24	2	-11	-6	-8	-25
1	25	1	-11	-5	-7	-23
1	25	2	-11	-5	-11	-27
1	26	1	0	2	-8	-6
1	26	2	-1	1	-6	-6
1	27	1	-4	-4	-5	-13
1	27	2	-8	-5	-9	-22
1	28	1	-10	-6	-8	-24
1	28	2	-11	-6	-8	-25
1	29	1	-7	-4	-6	-17
1	29	2	-8	-4	-7	-19
1	30	1	1	0	-6	-5
1	30	2	1	-2	-7	-8
1	32	1	-1	0	-1	-2
1	32	2	-5	0	-1	-6
1	33	1	0	0	0	0
1	33	2	0	0	0	0
1	34	1	-5	-1	0	-6
1	34	2	-3	-1	0	-4
1	35	1	0	0	0	0
1	35	2	0	0	0	0
1	36	1	-9	-6	-3	-18
1	36	2	-10	-5	-1	-16
1	38	1	-11	-5	-9	-25
1	38	2	-11	-6	-11	-27
1	39	1	-4	0	-3	-7
1	39	2	-5	0	-3	-8
1	40	1	-3	-3	-4	-10
1	40	2	-4	-1	-4	-9
1	41	1	-9	-5	-1	-15
1	41	2	-11	-6	-8	-25
1	42	1	-1	0	-7	-8
1	42	2	-2	1	-5	-6
1	43	1	0	2	0	2
1	43	2	0	2	0	2

1	44	1	-4	0	0	-4
1	44	2	-5	1	-1	-5
1	48	1	-8	-6	-8	-22
1	48	2	-2	-5	-9	-16
1	49	1	0	2	0	2
1	49	2	0	2	0	2
1	50	1	-3	0	0	-3
1	50	2	-1	0	0	-1
1	51	1	-3	-5	-5	-13
1	51	2	-4	-5	-5	-14
1	52	1	-4	-1	-8	-13
1	52	2	-4	-1	-8	-13
1	53	1	-7	-2	-2	-11
1	53	2	-7	-2	-2	-11
1	54	1	-5	-2	0	-7
1	54	2	-5	-3	0	-8
1	55	1	-7	-5	-10	-22
1	55	2	-8	-5	-9	-22
1	56	1	2	2	-9	-5
1	56	2	1	2	-8	-5
1	57	1	-9	-6	-8	-23
1	57	2	-10	-6	-7	-23
1	58	1	-10	-6	-7	-23
1	58	2	-11	-6	-7	-24
1	59	1	0	1	-2	-1
1	59	2	0	1	-2	-1
1	60	1	1	2	0	3
1	60	2	1	2	0	3

MHB scores for examiner one – OrthoAnalyzer™ models

Examiner	Subject number	Sample	MHB RHS	MHB Incisors	MHB LHS	MHB total
1	1	1	-6	0	-2	-8
1	1	2	-7	0	-2	-9
1	2	1	-6	1	0	-5
1	2	2	-6	0	0	-6
1	3	1	-1	0	0	-1
1	3	2	-1	-1	0	-2
1	5	1	-9	-6	-7	-22
1	5	2	-7	-6	-9	-22
1	6	1	-7	-1	-9	-17
1	6	2	-5	0	-8	-13
1	7	1	2	2	-3	1
1	7	2	1	2	-2	1
1	8	1	-1	-3	-3	-7
1	8	2	-2	-4	-4	-10
1	9	1	-8	-1	-6	-15
1	9	2	-7	-3	-8	-18
1	10	1	-3	-4	-8	-15
1	10	2	-2	-4	-8	-14
1	12	1	-2	0	-3	-5
1	12	2	-3	0	-3	-6
1	13	1	1	0	-3	-2
1	13	2	0	0	-2	-2
1	14	1	-1	-4	-5	-10
1	14	2	-3	-2	-7	-12
1	15	1	-2	-3	-3	-8
1	15	2	-3	-4	-5	-12
1	16	1	-1	2	0	1
1	16	2	-1	0	0	-1
1	17	1	0	0	-1	-1
1	17	2	0	0	-3	-3
1	18	1	-3	-4	-7	-14
1	18	2	-4	-4	-5	-13
1	19	1	0	2	0	2
1	19	2	0	2	0	2
1	20	1	0	2	0	2
1	20	2	1	2	0	3
1	21	1	-5	-6	-4	-15
1	21	2	-8	-6	-3	-17
1	22	1	-8	-6	-2	-16
1	22	2	-6	-6	-8	-20
1	23	1	0	0	-1	-1
1	23	2	0	0	0	0
1	24	1	-11	-6	-7	-24

1	24	2	-9	-6	-8	-23
1	25	1	-7	-6	-7	-20
1	25	2	-11	-6	-8	-25
1	26	1	0	0	-3	-3
1	26	2	0	0	-1	-1
1	27	1	-4	-5	-5	-18
1	27	2	-4	-6	-9	-19
1	28	1	-8	-6	-6	-20
1	28	2	-8	-6	-8	-22
1	29	1	-6	-4	-4	-14
1	29	2	-6	-4	-7	-17
1	30	1	0	0	-5	-5
1	30	2	0	0	-6	-6
1	32	1	0	0	-1	-1
1	32	2	0	0	-1	-1
1	33	1	0	0	0	0
1	33	2	0	0	0	0
1	34	1	-1	0	0	-1
1	34	2	-1	0	-1	-2
1	35	1	0	0	0	0
1	35	2	0	0	0	0
1	36	1	-7	-6	-2	-15
1	36	2	-8	-6	-2	-16
1	38	1	-9	-4	-8	-21
1	38	2	-9	-4	-8	-21
1	39	1	-4	0	-3	-7
1	39	2	-3	0	-2	-5
1	40	1	-3	-1	-2	-6
1	40	2	-3	-3	0	-6
1	41	1	-6	-6	-7	-19
1	41	2	-5	-4	-3	-12
1	42	1	-3	0	-4	-7
1	42	2	0	0	-6	-6
1	43	1	0	2	0	2
1	43	2	0	2	0	2
1	44	1	-3	1	0	-2
1	44	2	-4	2	0	-2
1	48	1	-7	-6	-8	-21
1	48	2	-7	-6	-8	-21
1	49	1	0	2	0	2
1	49	2	0	2	0	2
1	50	1	0	0	0	0
1	50	2	0	0	0	0
1	51	1	-2	-6	-6	-14
1	51	2	-4	-5	-5	-14
1	52	1	-4	-1	-8	-13

1	52	2	-4	-2	-8	-14
1	53	1	-6	-2	-1	-9
1	53	2	-6	-2	-3	-11
1	54	1	-4	-3	0	-7
1	54	2	-6	-2	0	-8
1	55	1	-8	-6	-10	-24
1	55	2	-9	-5	-9	-23
1	56	1	2	2	-7	-3
1	56	2	1	2	-9	-6
1	57	1	-8	-6	-6	-20
1	57	2	-8	-6	-8	-22
1	58	1	-10	-6	-7	-23
1	58	2	-10	-6	-7	-23
1	59	1	0	1	-2	-1
1	59	2	0	1	-2	-1
1	60	1	0	2	1	3
1	60	2	1	2	0	3

MHB scores for examiner one – Rhino plug-in

Examiner	Subject number	Examiner Sample	MHB RHS	MHB Incisors	MHB LHS	MHB total
1	1	1	-3	2	-2	-3
1	1	2	-3	1	-4	-6
1	2	1	-6	0	0	-6
1	2	2	-5	0	0	-5
1	3	1	-1	-2	0	-3
1	3	2	0	-2	-2	-4
1	5	1	-6	-5	-11	-22
1	5	2	-4	-5	-10	-19
1	6	1	-7	0	-8	-15
1	6	2	-7	0	-7	-14
1	7	1	3	2	-2	3
1	7	2	3	2	-3	2
1	8	1	-3	-4	-3	-10
1	8	2	-4	-4	-3	-11
1	9	1	-8	-4	-8	-20
1	9	2	-7	-4	-8	-19
1	10	1	-3	-6	-9	-18
1	10	2	-4	-5	-9	-18
1	12	1	-2	0	-3	-5
1	12	2	-2	0	-3	-5
1	13	1	1	0	-3	-2
1	13	2	-1	0	-3	-4
1	14	1	-4	-6	-7	-17
1	14	2	-4	-6	-8	-18
1	15	1	-3	-4	-8	-15
1	15	2	-4	-5	-8	-17
1	16	1	-1	1	2	2
1	16	2	-1	0	3	2
1	17	1	0	-2	-3	-5
1	17	2	0	-2	-4	-6
1	18	1	-5	-4	-7	-16
1	18	2	-5	-5	-7	-17
1	19	1	0	0	0	0
1	19	2	0	0	0	0
1	20	1	0	1	0	1
1	20	2	0	1	1	2
1	21	1	-8	-6	-2	-16
1	21	2	-9	-5	-7	-21
1	22	1	-9	-6	-8	-23
1	22	2	-9	-6	-9	-24
1	23	1	0	0	-2	-2
1	23	2	0	0	-2	-2
1	24	1	-10	-6	-6	-22

1	24	2	-9	-6	-6	-21
1	25	1	-9	-5	-11	-25
1	25	2	-9	-5	-10	-24
1	26	1	-2	2	-2	-2
1	26	2	-3	2	-2	-3
1	27	1	-4	-6	-12	-22
1	27	2	-4	-6	-11	-21
1	28	1	-12	-6	-10	-28
1	28	2	-12	-7	-10	-29
1	29	1	-7	-4	-6	-17
1	29	2	-7	-4	-6	-17
1	30	1	0	0	-7	-7
1	30	2	0	0	-6	-6
1	32	1	-3	0	-1	-4
1	32	2	-2	0	-2	-4
1	33	1	0	1	0	1
1	33	2	0	1	0	1
1	34	1	-6	-1	-1	-8
1	34	2	-5	-2	-1	-8
1	35	1	0	0	0	0
1	35	2	0	0	0	0
1	36	1	-7	-6	-4	-17
1	36	2	-7	-6	-5	-18
1	38	1	-12	-6	-12	-30
1	38	2	-11	-6	-11	-28
1	39	1	-4	0	-5	-9
1	39	2	-4	0	-5	-9
1	40	1	-2	-3	-4	-9
1	40	2	-2	-4	-3	-9
1	41	1	-6	-4	-4	-14
1	41	2	-6	-4	-6	-16
1	42	1	-1	0	-6	-7
1	42	2	-2	0	-6	-8
1	43	1	0	1	-2	-1
1	43	2	0	1	-3	-2
1	44	1	0	1	-2	-1
1	44	2	0	1	-2	-1
1	48	1	-4	-5	-9	-18
1	48	2	-4	-5	-9	-18
1	49	1	0	0	0	0
1	49	2	0	0	0	0
1	50	1	-4	0	0	-4
1	50	2	-4	0	0	-4
1	51	1	-5	-6	-4	-15
1	51	2	-5	-6	-4	-15
1	52	1	-6	-2	-9	-17

1	52	2	-6	-2	-10	-18
1	53	1	-9	-2	-3	-14
1	53	2	-9	-3	-2	-14
1	54	1	-9	-4	0	-13
1	54	2	-9	-5	0	-14
1	55	1	-11	-6	-12	-29
1	55	2	-11	-6	-12	-29
1	56	1	0	2	-9	-7
1	56	2	0	2	-9	-7
1	57	1	-8	-6	-10	-24
1	57	2	-8	-7	-10	-25
1	58	1	-11	-6	-10	-27
1	58	2	-12	-6	-10	-28
1	59	1	0	0	-1	-1
1	59	2	0	0	-2	-2
1	60	1	1	2	-1	2
1	60	2	1	2	-1	2

MHB scores for examiner two – PLASTER

Examiner	Subject number	Sample	MHB RHS	MHB Incisors	MHB LHS	MHB total
2	1	1	-6	-2	-3	-11
2	1	2	-7	-2	-5	-14
2	2	1	-5	1	0	-4
2	2	2	-5	1	0	-4
2	3	1	-1	-2	0	-3
2	3	2	-1	-1	0	-2
2	5	1	-10	-6	-8	-24
2	5	2	-8	-6	-9	-23
2	6	1	-7	-2	-8	-17
2	6	2	-7	-2	-9	-18
2	7	1	5	2	-4	3
2	7	2	3	2	-4	1
2	8	1	-1	-6	-6	-13
2	8	2	-5	-4	-3	-12
2	9	1	-10	-6	-9	-25
2	9	2	-9	-6	-9	-24
2	10	1	-3	-5	-9	-17
2	10	2	-2	-5	-9	-16
2	12	1	-4	-2	-1	-7
2	12	2	-3	0	-3	-6
2	13	2	0	2	-2	0
2	13	1	0	0	-3	-3
2	14	2	-2	-5	-5	-12
2	14	1	-2	-4	-6	-12
2	15	2	-6	-4	-6	-14
2	15	1	-6	-4	-5	-15
2	16	2	-1	1	2	2
2	16	1	-1	1	1	1
2	17	2	0	-2	-3	-5
2	17	1	0	-2	-3	-5
2	18	2	-3	-4	-8	-15
2	18	1	-3	-4	-8	-15
2	19	2	0	2	0	2
2	19	1	0	2	3	5
2	20	2	0	2	0	2
2	20	1	0	2	0	2
2	21	2	-8	-6	-4	-18
2	21	1	-8	-6	-5	-19
2	22	2	-9	-6	-7	-22
2	22	1	-9	-6	-8	-23
2	23	2	0	0	-1	-1
2	23	1	0	0	-2	-2
2	24	2	-11	-6	-8	-25

2	24	1	-11	-6	-9	-26
2	25	2	-10	-6	-11	-27
2	25	1	-11	-6	-11	-28
2	26	2	-1	2	-5	-4
2	26	1	-2	0	-7	-9
2	27	2	-8	-4	-9	-21
2	27	1	-8	-4	-9	-21
2	28	2	-9	-6	-8	-23
2	28	1	-9	-6	-8	-23
2	29	2	-7	-4	-8	-19
2	29	1	-7	-4	-7	-18
2	30	2	1	-2	-7	-8
2	30	1	1	0	-8	-7
2	32	2	-4	0	-3	-7
2	32	1	-2	0	-1	-3
2	33	2	0	0	0	0
2	33	1	0	0	0	0
2	34	2	-5	-2	0	-7
2	34	1	-4	-1	0	-5
2	35	2	0	0	0	0
2	35	1	0	0	0	0
2	36	2	-7	-6	-6	-19
2	36	1	-9	-6	-2	-17
2	38	2	-11	-6	-9	-26
2	38	1	-11	-5	-9	-25
2	39	2	-7	0	-3	-10
2	39	1	-5	0	-6	-11
2	40	2	-3	-2	4	-9
2	40	1	-5	-2	-4	-11
2	41	2	-10	-4	-3	-17
2	41	1	-10	-6	-5	-21
2	42	2	-1	-2	-7	-10
2	42	1	0	-2	-8	-10
2	43	2	0	2	0	2
2	43	1	0	2	0	2
2	44	2	-4	0	0	-4
2	44	1	-4	0	0	-4
2	48	2	-3	-4	-8	-15
2	48	1	-3	-6	-8	-17
2	49	2	0	2	0	2
2	49	1	0	2	0	2
2	50	2	-4	-2	-3	-9
2	50	1	-4	-2	-1	-7
2	51	1	-5	-5	-6	-16
2	51	2	-8	-4	-4	-16
2	52	1	-4	-1	-9	-14

2	52	2	-4	-2	-9	-15
2	53	1	-7	-2	-3	-12
2	53	2	-7	-2	-3	-12
2	54	1	-6	-1	0	-7
2	54	2	-7	-4	0	-11
2	55	1	-10	-4	-9	-23
2	55	2	-9	-4	-9	-22
2	56	1	1	2	-8	-5
2	56	2	1	2	-9	-6
2	57	1	-9	-6	-8	-23
2	57	2	-9	-6	-7	-22
2	58	1	-11	-6	-7	-24
2	58	2	-11	-6	-7	-24
2	59	1	-1	2	-2	-1
2	59	2	0	1	-2	-1
2	60	1	0	1	-1	0
2	60	2	0	2	-1	1

MHB scores for examiner two – OrthoAnalyzer™ models

Examiner	Subject number	Sample	MHB RHS	MHB Incisors	MHB LHS	MHB total
2	1	1	-8	0	-6	-14
2	1	2	-10	0	-2	-12
2	2	1	-6	1	0	-5
2	2	2	-5	0	0	-5
2	3	1	-1	0	0	-1
2	3	2	-1	0	0	-1
2	5	1	-6	-6	-10	-22
2	5	2	-7	-6	-10	-23
2	6	1	-7	-2	-4	-13
2	6	2	-7	-2	-3	-12
2	7	1	0	2	-1	1
2	7	2	3	2	-2	3
2	8	1	-3	-6	-3	-12
2	8	2	-3	-2	-3	-8
2	9	1	-7	-2	-3	-12
2	9	2	-9	-1	-6	-16
2	10	1	-3	-4	-9	-16
2	10	2	-2	-4	-8	-14
2	12	1	-4	-1	-4	-9
2	12	2	-3	0	-3	-6
2	13	1	1	0	-1	0
2	13	2	0	0	-1	-1
2	14	1	-2	-4	-6	-12
2	14	2	-2	-4	-6	-12
2	15	1	-8	-4	-4	-16
2	15	2	-8	-4	-5	-17
2	16	1	1	2	1	4
2	16	2	-2	1	1	0
2	17	1	0	-2	-2	-4
2	17	2	0	-2	-2	-4
2	18	1	-7	-4	-7	-18
2	18	2	-2	-4	-7	-13
2	19	1	0	2	0	2
2	19	2	0	0	0	0
2	20	1	0	0	0	0
2	20	2	0	0	0	0
2	21	1	-7	-6	-5	-18
2	21	2	-8	-6	-9	-23
2	22	1	-8	-6	-8	-22
2	22	2	-8	-6	-8	-22
2	23	1	0	0	-2	-2
2	23	2	0	0	-1	-1
2	24	1	-11	-6	-10	-27

2	24	2	-11	-6	-10	-27
2	25	1	-11	-4	-11	-26
2	25	2	-11	-4	-11	-26
2	26	1	-4	-2	-8	-14
2	26	2	-4	-2	-8	-14
2	27	1	-8	-4	-9	-21
2	27	2	-8	-4	-9	-21
2	28	1	-8	-6	-8	-22
2	28	2	-8	-6	-8	-22
2	29	1	-8	-4	-8	-20
2	29	2	-7	-2	-5	-14
2	30	1	1	0	-7	-6
2	30	2	1	0	-7	-6
2	32	1	0	-2	-2	-4
2	32	2	0	0	-1	-1
2	33	1	0	0	0	0
2	33	2	0	0	0	0
2	34	1	-1	-2	0	-3
2	34	2	-3	0	0	-3
2	35	1	0	0	0	0
2	35	2	0	0	0	0
2	36	1	-5	-4	-6	-15
2	36	2	-8	-4	-5	-17
2	38	1	-8	-4	9	-21
2	38	2	-9	-4	-8	-21
2	39	1	-8	0	-8	-16
2	39	2	-6	0	-4	-10
2	40	1	-3	0	-4	-7
2	40	2	-3	-2	-4	-9
2	41	1	-8	-5	-8	-21
2	41	2	-9	-6	-8	-23
2	42	1	0	-2	-5	-7
2	42	2	0	0	-8	-8
2	43	1	0	2	0	2
2	43	2	0	2	0	2
2	44	1	-2	0	0	-2
2	44	2	-4	0	-1	-5
2	48	1	-8	-4	-8	-20
2	48	2	-8	-4	-8	-20
2	49	1	0	0	0	0
2	49	2	0	0	0	0
2	50	1	-1	-2	0	-3
2	50	2	-2	-2	0	-4
2	51	1	-6	-4	-7	-17
2	51	2	-5	-5	-6	-16
2	52	1	-4	-1	-9	-14

2	52	2	-6	-1	-9	-16
2	53	1	-6	-1	-4	-11
2	53	2	-7	-2	-6	-15
2	54	1	-6	-2	0	-8
2	54	2	-6	-4	-2	-12
2	55	1	-8	-5	-10	-23
2	55	2	-9	-5	-9	-23
2	56	1	1	2	-9	-6
2	56	2	1	2	-9	-6
2	57	1	-7	-6	-8	-21
2	57	2	-9	-6	-10	-25
2	58	1	-11	-6	-7	-24
2	58	2	-11	-6	-8	-25
2	59	1	0	1	-2	-1
2	59	2	0	-1	-2	-3
2	60	1	0	0	-1	-1
2	60	2	0	1	-1	0

MHB scores for examiner two – Rhino plug-in

Examiner	Subject number	Examiner Sample	MHB RHS	MHB Incisors	MHB LHS	MHB total
2	1	1	-4	1	-3	-6
2	1	2	-3	2	-4	-5
2	2	1	-5	0	0	-5
2	2	2	-6	0	0	-6
2	3	1	-1	-2	0	-3
2	3	2	-2	-2	0	-4
2	5	1	-7	-5	-10	-22
2	5	2	-6	-5	-11	-22
2	6	1	-6	-1	-9	-16
2	6	2	-7	0	-8	-15
2	7	1	3	2	-4	1
2	7	2	-3	2	3	2
2	8	1	-4	-4	-3	-11
2	8	2	-4	-4	-3	-11
2	9	1	-8	-4	-8	-20
2	9	2	-8	-4	-8	-20
2	10	1	-3	-4	-9	-16
2	10	2	-3	-4	-9	-16
2	12	1	-1	0	-4	-5
2	12	2	-1	0	-5	-6
2	13	1	0	0	-3	-3
2	13	2	0	0	-4	-4
2	14	1	-4	-6	-8	-18
2	14	2	-2	-6	-8	-16
2	15	1	-3	-4	-8	-15
2	15	2	-3	-6	-8	-17
2	16	1	-1	1	2	2
2	16	2	-1	2	2	3
2	17	1	-2	-1	-4	-7
2	17	2	0	-1	-4	-5
2	18	1	-5	-6	-6	-17
2	18	2	-5	-6	-7	-18
2	19	1	-1	1	0	0
2	19	2	0	1	0	1
2	20	1	1	0	-2	-1
2	20	2	1	0	0	1
2	21	1	-8	-6	-4	-18
2	21	2	-8	-6	-1	-15
2	22	1	-9	-6	-9	-24
2	22	2	-7	-6	-7	-20
2	23	1	0	0	-2	-2
2	23	2	0	0	-1	-1
2	24	1	-12	-6	-11	-29

2	24	2	-12	-6	-10	-28
2	25	1	-12	-5	-11	-28
2	25	2	-12	-5	-7	-24
2	26	1	1	2	-2	1
2	26	2	0	2	-3	-1
2	27	1	-3	-5	-12	-20
2	27	2	-4	-5	-8	-17
2	28	1	-8	-6	-7	-21
2	28	2	-8	-6	-7	-21
2	29	1	-8	-4	-7	-19
2	29	2	-8	-4	-7	-19
2	30	1	0	0	-7	-7
2	30	2	0	0	-7	-7
2	32	1	-2	0	-2	-4
2	32	2	-3	0	-1	-4
2	33	1	1	1	0	2
2	33	2	1	1	0	2
2	34	1	-3	-1	-1	-5
2	34	2	-5	-1	0	-6
2	35	1	0	0	0	0
2	35	2	0	0	0	0
2	36	1	-9	-6	-3	-18
2	36	2	-6	-5	-5	-16
2	38	1	-11	-6	-12	-29
2	38	2	-12	-6	-12	-30
2	39	1	-4	0	-4	-8
2	39	2	-4	0	-4	-8
2	40	1	-2	-4	-4	-10
2	40	2	-3	-2	-4	-9
2	41	1	-5	-4	-5	-14
2	41	2	-7	-5	-5	-17
2	42	1	-1	0	-8	-9
2	42	2	0	0	-8	-8
2	43	1	0	2	-2	0
2	43	2	0	2	1	3
2	44	1	-4	1	0	-3
2	44	2	-4	1	0	-3
2	48	1	-2	-5	-9	-16
2	48	2	-3	5	-10	-18
2	49	1	1	0	0	1
2	49	2	0	0	0	0
2	50	1	-4	0	0	-4
2	50	2	-6	0	0	-6
2	51	1	-3	-6	-5	-14
2	51	2	-6	-6	-4	-16
2	52	1	-4	-2	-9	-15

2	52	2	-5	-2	-9	-16
2	53	1	-10	-2	-3	-15
2	53	2	-9	-2	-3	-14
2	54	1	-4	-4	0	-8
2	54	2	-5	-4	0	-9
2	55	1	-10	-6	-12	-28
2	55	2	-9	-6	-12	-27
2	56	1	1	2	-8	-5
2	56	2	0	2	-8	-6
2	57	1	-8	-6	-10	-24
2	57	2	-11	-6	-10	-26
2	58	1	-11	-6	-10	-27
2	58	2	-11	-6	-9	-26
2	59	1	-2	0	-1	-3
2	59	2	-1	0	-2	-3
2	60	1	1	2	-1	2
2	60	2	1	2	-1	2

MHB scores for examiner three – PLASTER

Examiner	Subject number	Sample	MHB RHS	MHB Incisors	MHB LHS	MHB total
3	1	1	-6	0	-3	-9
3	1	2	-5	1	-5	-9
3	2	1	-4	1	0	-3
3	2	2	-8	1	4	-3
3	3	1	-1	0	0	-1
3	3	2	-1	0	0	-1
3	5	1	-9	-6	-8	-23
3	5	2	-11	-6	-9	-26
3	6	1	-6	0	-9	-15
3	6	2	-7	-2	-9	-18
3	7	1	4	2	-4	2
3	7	2	4	2	-3	3
3	8	1	-1	-6	-5	-12
3	8	2	-1	-6	-4	-11
3	9	1	-10	-6	-10	-26
3	9	2	-11	-6	-9	-26
3	10	1	-2	-6	-10	-18
3	10	2	-3	-5	-10	-18
3	12	1	-2	-1	-5	-8
3	12	2	-5	1	-1	-5
3	13	1	1	2	-3	0
3	13	2	1	0	-4	-3
3	14	1	-5	-6	-7	-18
3	14	2	-3	-5	-6	-14
3	15	1	-2	-6	-8	-16
3	15	2	-6	-6	-5	-17
3	16	1	-1	2	2	3
3	16	2	-1	2	2	3
3	17	1	0	-1	-2	-3
3	17	2	0	-2	-2	-4
3	18	1	-3	-6	-8	-17
3	18	2	-4	-6	-7	-17
3	19	1	0	0	0	0
3	19	2	4	2	4	10
3	20	1	0	2	0	2
3	20	2	3	2	3	8
3	21	1	-6	-6	-5	-17
3	21	2	-9	-6	-3	-18
3	22	1	-9	-6	-6	-21
3	22	2	-10	-6	-8	-24
3	23	1	0	0	-1	-1
3	23	2	0	0	-1	-1
3	24	1	-11	-6	-8	-25

3	24	2	-11	-6	-9	-26
3	25	1	-11	-6	-11	-28
3	25	2	-10	-5	-11	-26
3	26	1	-3	0	-7	-10
3	26	2	-2	2	-7	-7
3	27	1	-5	-6	-9	-20
3	27	2	-5	-6	-10	-21
3	28	1	-9	-6	-7	-22
3	28	2	-12	-6	-7	-25
3	29	1	-8	-4	-7	-19
3	29	2	-8	-4	-7	-19
3	30	1	2	0	-9	-7
3	30	2	1	-2	-8	-9
3	32	1	-2	0	-2	-4
3	32	2	-2	0	-1	-3
3	33	1	0	0	0	0
3	33	2	1	2	0	3
3	34	1	-3	0	0	-3
3	34	2	-3	0	0	-3
3	35	1	2	0	1	3
3	35	2	3	0	2	5
3	36	1	-9	-6	-2	-17
3	36	2	-8	-6	-6	-20
3	38	1	-11	-6	-9	-26
3	38	2	-11	-5	-10	-26
3	39	1	-3	0	-5	-8
3	39	2	-6	0	-5	-11
3	40	1	-1	-3	-4	-8
3	40	2	-3	-2	-4	-9
3	41	1	-11	-6	1	-16
3	41	2	-10	-6	0	-16
3	42	1	-3	0	-9	-12
3	42	2	-1	0	-10	-11
3	43	1	0	2	0	2
3	43	2	0	2	1	3
3	44	1	-6	2	-2	-6
3	44	2	-5	1	-3	-7
3	48	1	-2	-6	-9	-17
3	48	2	-4	-6	-9	-19
3	49	1	0	2	1	3
3	49	2	1	2	4	7
3	50	1	-3	0	0	-3
3	50	2	-1	0	-4	-5
3	51	1	-4	-6	-4	-14
3	51	2	-8	-6	-5	-19
3	52	1	-3	0	-8	-11

3	52	2	-3	-1	-9	-13
3	53	1	-7	-2	-2	-11
3	53	2	-7	-2	-3	-12
3	54	1	-5	-4	0	-9
3	54	2	-4	-3	0	-7
3	55	1	-8	-6	-10	-24
3	55	2	-7	-6	-11	-24
3	56	1	1	2	-9	-6
3	56	2	0	2	-9	-7
3	57	1	-9	-6	-9	-24
3	57	2	-10	-6	-8	-24
3	58	1	-11	-6	-8	-25
3	58	2	-11	-6	-9	-26
3	59	1	-1	1	-2	-2
3	59	2	-1	0	-2	-3
3	60	1	1	2	1	4
3	60	2	4	2	1	7

MHB scores for examiner three – OrthoAnalyzer™ models

Examiner	Subject number	Sample	MHB RHS	MHB Incisors	MHB LHS	MHB total
3	1	1	-9	0	-3	-12
3	1	2	-6	0	-2	-8
3	2	1	-4	1	-2	-5
3	2	2	-5	1	0	-4
3	3	1	-2	0	0	-2
3	3	2	-1	0	0	-1
3	5	1	-10	-6	-11	-27
3	5	2	-9	-6	-10	-25
3	6	1	-9	-1	-7	-17
3	6	2	-7	-1	-8	-16
3	7	1	1	2	-2	1
3	7	2	3	2	-2	3
3	8	1	-4	-6	-3	-13
3	8	2	-4	-6	-2	-12
3	9	1	-11	-6	-9	-26
3	9	2	-10	-6	-2	-18
3	10	1	-3	-6	-10	-19
3	10	2	-3	-5	-9	-17
3	12	1	-4	-1	-2	-7
3	12	2	-1	-1	-2	-4
3	13	1	1	2	-2	1
3	13	2	1	2	-4	-1
3	14	1	-5	-6	-8	-19
3	14	2	-1	-5	-7	-13
3	15	1	-7	-5	-6	-18
3	15	2	-6	-5	-5	-16
3	16	1	-1	2	1	2
3	16	2	0	2	2	4
3	17	1	-1	-2	-2	-5
3	17	2	0	-1	-2	-3
3	18	1	-7	-6	-6	-19
3	18	2	-4	-6	-7	-17
3	19	1	0	2	0	2
3	19	2	3	2	3	8
3	20	1	0	2	0	2
3	20	2	1	2	1	4
3	21	1	-8	-6	-5	-19
3	21	2	-8	-6	-7	-21
3	22	1	-9	-6	-9	-24
3	22	2	-9	-6	-9	-24
3	23	1	0	0	-1	-1
3	23	2	-1	0	0	-1
3	24	1	-12	-6	-9	-27

3	24	2	-11	-6	-8	-25
3	25	1	-11	-6	-11	-28
3	25	2	-11	-5	-11	-27
3	26	1	-3	0	-8	-11
3	26	2	0	0	-8	-8
3	27	1	-6	-4	-11	-21
3	27	2	-7	-5	-9	-21
3	28	1	-8	-6	-8	-22
3	28	2	-9	-6	-8	-23
3	29	1	-7	-6	-10	-23
3	29	2	-8	-5	-9	-22
3	30	1	1	0	-8	-7
3	30	2	4	0	-6	-2
3	32	1	-1	0	-4	-5
3	32	2	-2	0	-4	-6
3	33	1	0	0	0	0
3	33	2	3	2	1	6
3	34	1	-4	-1	0	-5
3	34	2	-4	0	0	-4
3	35	1	0	0	0	0
3	35	2	1	0	1	2
3	36	1	-7	-6	-4	-17
3	36	2	-9	-6	-5	-20
3	38	1	-11	-6	-10	-27
3	38	2	-10	-6	-8	-24
3	39	1	-7	0	-7	-14
3	39	2	-4	1	-7	-10
3	40	1	-5	-3	-6	-14
3	40	2	-2	-2	-5	-9
3	41	1	-9	-6	-8	-23
3	41	2	-10	-6	-8	-24
3	42	1	-3	0	-8	-11
3	42	2	-3	0	-9	-12
3	43	1	0	2	0	2
3	43	2	3	2	4	9
3	44	1	-6	2	1	-3
3	44	2	-6	2	1	-3
3	48	1	-6	-6	-8	-20
3	48	2	-8	-5	-9	-22
3	49	1	0	2	0	2
3	49	2	1	2	1	4
3	50	1	-2	0	-1	-3
3	50	2	-2	1	0	-1
3	51	1	-6	-6	-2	-14
3	51	2	-7	-6	-4	-17
3	52	1	-6	-1	-9	-16

3	52	2	-5	-2	-9	-16
3	53	1	-6	-3	-3	-12
3	53	2	-8	-3	-4	-15
3	54	1	-5	-6	-2	-13
3	54	2	-4	-4	0	-8
3	55	1	-8	-6	-11	-25
3	55	2	-8	-6	-9	-23
3	56	1	1	2	-9	-6
3	56	2	1	2	-8	-5
3	57	1	-11	-6	-10	-27
3	57	2	-9	-6	-8	-23
3	58	1	-11	-6	-8	-25
3	58	2	-11	-6	-6	-23
3	59	1	-3	-1	-3	-7
3	59	2	0	0	-3	-3
3	60	1	1	2	-4	-1
3	60	2	4	2	0	6

MHB scores for examiner three – Rhino plug-in

Examiner	Subject number	Sample	MHB RHS	MHB Incisors	MHB LHS	MHB total
3	1	1	-3	0	-3	-6
3	1	2	-3	0	-2	-5
3	2	1	0	0	-6	-6
3	2	2	0	0	-6	-6
3	3	1	0	-2	-1	-3
3	3	2	0	-1	-2	-3
3	5	1	-11	-5	-4	-20
3	5	2	-10	-5	-5	-20
3	6	1	-9	0	-6	-15
3	6	2	-9	0	-6	-15
3	7	1	-4	2	3	1
3	7	2	-4	2	3	1
3	8	1	-4	-4	-2	-10
3	8	2	-4	-4	-2	-10
3	9	1	-9	-4	-8	-21
3	9	2	-8	-4	-8	-20
3	10	1	-9	-4	-2	-15
3	10	2	-9	-4	-2	-15
3	12	1	-4	0	-1	-5
3	12	2	-4	0	-1	-5
3	13	1	-3	0	0	-3
3	13	2	-3	0	1	-2
3	14	1	-8	-6	-1	-15
3	14	2	-7	-6	-5	-18
3	15	1	-7	-4	-3	-14
3	15	2	-7	-4	-3	-14
3	16	1	2	2	-1	3
3	16	2	2	2	-2	2
3	17	1	-4	-1	-2	-7
3	17	2	-4	-1	-2	-7
3	18	1	-7	-6	-4	-17
3	18	2	-7	-6	-3	-16
3	19	1	0	0	0	0
3	19	2	0	1	0	1
3	20	1	0	1	3	4
3	20	2	0	1	3	4
3	21	1	-2	-6	-8	-16
3	21	2	-2	-6	-8	-16
3	22	1	8	-6	-8	-26
3	22	2	-9	-6	-8	-23
3	23	1	-1	0	0	-1
3	23	2	-1	0	0	-1
3	24	1	-9	-6	-11	-26

3	24	2	-10	-6	-11	-27
3	25	1	-11	-5	-7	-23
3	25	2	-11	-5	-8	-24
3	26	1	-2	2	1	1
3	26	2	-2	2	1	1
3	27	1	-8	-5	-3	-16
3	27	2	-9	-5	-3	-17
3	28	1	-10	-6	-8	-24
3	28	2	-10	-6	-8	-24
3	29	1	-6	-4	-4	-14
3	29	2	-7	-4	-4	-15
3	30	1	-8	0	0	-8
3	30	2	-7	0	0	-7
3	32	1	-2	0	-2	-4
3	32	2	-1	0	-2	-3
3	33	1	0	1	2	3
3	33	2	0	1	1	2
3	34	1	-2	-1	-3	-6
3	34	2	-1	-1	-3	-5
3	35	1	0	0	1	1
3	35	2	0	0	0	0
3	36	1	-3	-6	-9	-18
3	36	2	-3	-6	-9	-18
3	38	1	-12	-6	-11	-29
3	38	2	-12	-6	-10	-28
3	39	1	-4	0	-4	-8
3	39	2	-6	0	-2	-8
3	40	1	-5	-4	-1	-10
3	40	2	-7	-3	-2	-12
3	41	1	-5	-4	-4	-13
3	41	2	-5	-4	-4	-13
3	42	1	-8	0	1	-7
3	42	2	-6	0	1	-5
3	43	1	0	2	-2	0
3	43	2	0	2	0	2
3	44	1	0	0	-4	-4
3	44	2	0	1	-5	-4
3	48	1	-11	-5	0	-16
3	48	2	-10	-5	-1	-16
3	49	1	0	0	0	0
3	49	2	0	0	0	0
3	50	1	0	0	-3	-3
3	50	2	0	0	-3	-3
3	51	1	-5	-6	-7	-18
3	51	2	-5	-6	-6	-17
3	52	1	-10	-2	-4	-16

3	52	2	-9	-2	-4	-15
3	53	1	-3	-2	-7	-12
3	53	2	-3	-2	-8	-13
3	54	1	0	-3	-2	-5
3	54	2	0	-3	-2	-5
3	55	1	-12	-6	-8	-26
3	55	2	-12	-6	-8	-26
3	56	1	-8	2	1	-5
3	56	2	-8	2	1	-5
3	57	1	-11	-6	-9	-26
3	57	2	-10	-6	-9	-25
3	58	1	-10	-6	-11	-27
3	58	2	-9	-6	-11	-26
3	59	1	-1	0	-1	-2
3	59	2	-1	0	-1	-2
3	60	1	-2	2	1	1
3	60	2	-1	2	1	2

Appendix VIII.

Journal articles that have been published or submitted by the author, as a result of research in this field.

1. E Chalmers, G McIntyre, W Wang, T Gillgrass, C Martin, P Mossey. Intraoral 3D scanning or dental impressions for the assessment of dental arch relationships in cleft care: which is superior? Submitted to the Cleft Palate – Craniofacial Journal 2015.

2. C Martin, E Chalmers, G McIntyre, H Cochrane & P Mossey. Orthodontic scanners: what's available? Journal of orthodontics 2015; 42: 136-143.

3. X Ma, C Martin, G McIntyre, P Lin, P Mossey. Digital three-dimensional automation of the modified Huddart and Bodenham scoring system for patients with cleft lip and palate. Draft manuscript 2015.